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Phosphorus	0.620	0.392	0.125	0.093	0.093	0.180
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Vitamin C	—*	—*	—*	—*	—*	—*
Vitamin D	—**	—**	—**	—**	—**	—**
Vitamin E	+ + +	+ +	—	—	— to +	+
Vitamin G	+ + +	+	— to +	+	+ +	+
Moisture	7.0	8.0	10.90	35.30	87.00	73.70
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The Journal of Pediatrics

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X-RAY SHADOWS IN GROWING BONES PRODUCED BY LEAD; THEIR CHARACTERISTICS, CAUSE, ANATOMICAL COUNTERPART IN THE BONE AND DIFFERENTIATION

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AT ABOUT the same time Park, Jackson and Kajdi (1930, 1931),[1, 2] Vogt (1930, 1932),[3, 4] Caffey (1931),[5] and Koga, Kitamura and Sato (1931),* all independently reported that in the x-ray films of the skeletons of children suffering from lead poisoning, significant shadows make their appearance in the newly forming bone adjacent to the growing cartilage. More recently Kasahara and Hiroshima (1932),[6] and Kraft and Kato (1932)[7] have published confirmatory observations.

During the summer of 1932 an outbreak of lead poisoning occurred in Baltimore as the result of the use as fuel of discarded rubber battery casings which, in the process of use, had become permeated with lead. The poisoning was due to the inhalation of lead-containing fumes and probably also to the ingestion of lead in the food contaminated from the dust. An account of this outbreak, which was studied by Williams, Schulze, Rothschild, Brown and Smith,[8] has just been published. The x-ray films of the bones of the children poisoned by lead in this outbreak have furnished an unusual opportunity to study the shadows produced by lead in the bones. Moreover, we have now had the opportunity to observe the histologic changes caused by lead in the bones in a series of seven children and, in consequence, are able

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The anatomical investigations were aided as the result of a grant from the American Medical Association for a special bone saw.

*Kasahara and Hiroshima state that Koga, Kitamura and Sato described the characteristic x-ray shadows produced by lead at the ends of the bones of the extremities in 1931 in the Japanese tongue. They do not give the reference.

to give a better description of those changes than was possible previously. The present paper, therefore, deals in detail with the characteristics of the shadows produced by lead in the growing skeleton and gives an accurate description of the pathologic condition underlying the shadows. Moreover, it discusses shadows which develop at the growing ends of the long bones from other causes and which might be confounded with the lead shadows.

THE SHADOWS IN THE BONES

The shadows in the bones produced by lead are difficult to describe, because they vary so much in different cases, not only with the severity, duration and time of occurrence of the poisoning but with the rapidity of growth of the bone at the time when the poisoning was in progress.

The shadows always develop at the cartilage-shaft junction. Accordingly, if the x-ray film is taken while the poisoning is in progress, the shadow will be found at the extreme end of the shaft. If, on the other hand, the poisoning took place some time previously, the shadow will be found at a variable distance from the end, the distance being determined by the amount of new bone which has formed in the course of growth.

As was pointed out originally by Pommer,[9] and in more detail by Schmorl,[10] and as has been recently reemphasized by Park,[11] the rate of growth at the different cartilage-shaft junctions of the long bones at any given age period is subject to great variation. In early childhood the order of rapidity of growth, is as follows: the middle ribs; the lower end of the femur; the upper end of the femur; the upper end of the humerus, together with both ends of the tibia and fibula; the lower ends of the radius and ulna; the lower end of the humerus; the upper end of the radius; the upper end of the ulna. This variability in the rate of growth at the different ends of the long bones modifies the lead zones in two ways; it causes them to vary in thickness and also in the position which they occupy with reference to the end of the shaft. The more rapid the growth at the cartilage-shaft junction, the broader the lead zone; conversely, the slower the growth, the narrower the zone, until at the slowest growing cartilage-shaft junctions the zone does not exceed the thickness of a line. Similarly, if an interval has elapsed since the poisoning stopped, the zone will lie farthest from the end of the shaft at those ends where growth is taking place fastest and, conversely, will lie closest to the end of the shaft where growth is slowest. Knowledge of these facts explains why the lead bands are more conspicuous at certain cartilage-shaft junctions than at others and why at some they are not readily seen or do not appear at all. In the fast growing end of a bone, like the lower end of the femur, for example, the zone may be 2.5 centimeters thick or it may lie a centimeter or more from the end of the shaft, whereas at the upper end of the radius the band may

not be developed sufficiently to show at all, or, merely a line in thickness, it may be situated so close to the cartilage-shaft junction as not to be readily distinguishable from the bright line which marks the latter. To illustrate, in the case of F. S., (H. L. 58566), aged eight and one-half years, the breadth of the lead zone at the lower end of the femur was 2.5 centimeters, at the upper tibia 1.7 centimeters, at the lower tibia 1.2 centimeters, at the lower radius 1 centimeter. The lower end of the humerus and the upper ends of the radius and ulna failed to show any distinct line. In the case of M. J. (H. L. 79225), aged six years, the lead zones, not more than 2 millimeters in thickness, could be readily seen about 1 centimeter above the lower ends of the shafts of the radius and ulna and about 1.3 centimeters from the upper end of the humerus. Zones in the form of lines were visible 1 to 2 millimeters from the distal cartilage-shaft junctions of the four inner metacarpal bones. The vestige of a zone in the form of a broken line could be seen a few millimeters from the upper end of the shaft of the radius. No line could be seen at the upper end of the ulna.

The intensity and the finer structure of the shadows are also subject to great variations in different cases. When the poisoning is intense and lasts to the time when the patient comes under observation, the shadow appears as a sharply defined homogeneous band of metallic-like density, lying across the extreme end of the shaft. Finer structure in the zone cannot be distinguished and the transition to the normal bone is sharp. For example, in the case of N. M. (H. L. 79258), one year old, exposed for five months to the fumes of lead-containing battery casings, the lower ends of the radius and ulna were marked by snowy white bands 1.5 millimeters in thickness. The finer structure in these bands was not visible. Their demarcation from the shaft proper was clear-cut. In this case the distal ends of the metacarpal bones of the fingers, the proximal end of the metacarpal bone of the thumb and the proximal ends of the proximal and middle phalanges were delineated by silvery lines. The upper end of the radius was also marked by a distinct lead zone but the upper end of the ulna showed merely a silvery penciling.

When the lead poisoning has continued to the time of the picture, so that the zones lie at the extreme ends of the shafts, they have this homogeneous metallic character. When, however, the poisoning had stopped long enough before the x-ray film was taken for new bone to form, the appearance is quite different. The lead zone is no longer dense; its finer structure is visible and its demarcation from the adjacent bone on both sides is indistinct. In such cases the zone can be seen to be composed of trabeculae which appear more numerous and brighter than the adjacent ones. Moreover, the trabeculae in the lead zone shade off into the trabeculae of the adjacent normal bone with which they are continuous. From the x-ray films alone one perceives that the cause of the shadow in the lead zone is the superimposition of the

shadows of trabeculae, which are both more numerous and brighter than the shadows of the trabeculae in the normal parts. The cause of the lack of sharp definition of the lead zone after the end of the shaft has grown beyond it is the shading off of the constituent trabecular shadows. In these two respects the band produced by lead furnishes a contrast to the band produced by elementary phosphorus. The phosphorus band is extremely dense, so dense that its finer structure does not appear, and it is sharply demarcated from the adjacent normal bone. The differences

Fig. 1.—N. M. (H. L. 79258), aged one year, was exposed for five months, up to the time when the film was taken, to the fumes of burning battery casings. The lower ends of radius and ulna are marked by terminal bands 1.5 mm. thick which, in the x-ray film, were snowy white. The metacarpal bones and phalanges showed intensification of the shadows marking the epiphyseo-diaphyseal junctions. The upper end of the radius shows a thin zone of increased density but the upper end of the ulna shows none. Only the bands at the lower ends of the radius and ulna are characteristic.

are so striking that one could infer from the study of the shadows alone that the phosphorus effect develops suddenly and fully and stops abruptly and completely, whereas in the case of lead one is compelled to infer that the effect on the bone continues for a time after the lead has ceased to find its way into the body. The reason that the zone produced by lead at the end of the shaft is so much denser than the older one which has become separated from the end is that the deposition of

lead is at its heaviest at the end, because of the great quantities of matrix substance of the cartilage which is there present. Another reason is that normally the end of the shaft casts a heavy shadow and forms a substratum of density which the lead shadow merely increases. The reason the lead zone in the substance of the bone away from the end of the shaft is less dense is that in the first place it stands by itself and in the second place, as the lead formation ages, it keeps thinning from action upon it of the normally active destructive forces of the shaft.

The shadows vary greatly, therefore, in different cases. In many children suffering from lead poisoning the shadows are so faint, even at the fast growing ends of the long bones, that one is in doubt whether to regard them as lead zones or merely abnormally dense terminations of normal bones such as are seen in older children or in infants who have received viosterol. On the other hand, the zones may be so definite and characteristic as to leave little doubt in regard to their true nature. In some cases in which the lead shadows are light they seem to resolve themselves on close inspection into a series of transverse lines. Transverse lines in bones denote sudden cessations of growth. The relationship of transverse lines to growth has been proved experimentally by Asada[12] and inferred by Harris[13, 14] and by Eliot, Souther and Park.[15] The general principles of the mechanism of their production has been described by the authors last mentioned. Sudden interruptions of growth, giving rise to transverse lines, are exceedingly common and must often occur in lead poisoning, so that one need not be surprised at finding them. When such lines are visible, the lead zone is almost always poorly developed. Faint zones often appear more distinct when one looks at the film from a distance of several feet.

The lead zones are best developed and therefore most conspicuous at the lower ends of the radius and ulna, the lower end of the femur and at both ends of the tibia and fibula. They are, of course, especially well developed at the anterior endings of the ribs but in the living subject are not so readily visible because of the conflicting shadows of the thoracic cage and its contents. As in the case of transverse lines in general the lead zones will be best developed when the plane formed by the epiphyseo-diaphyseal junction is at right angles to the long axis of the shaft, because under such circumstances there is the best superimposition. When the surface of the epiphyseo-diaphyseal junction is curved as in the case of the upper end of the humerus and the upper and lower ends of the femur, superimposition is interfered with and the shadow is apt to be less clearly defined. For these reasons the shadows in lead poisoning are especially clear and sharp at the lower end of the radius and the two ends of the tibia. Just as in transverse line formation due to interruptions of growth, the shadow in lead poisoning is less well developed at the lower end of the ulna than the lower end of the radius and, possibly because of the slenderness of the bone, is not particularly well

developed at the lower end of the fibula. If the lead poisoning has been sufficiently intense and prolonged, the lead zones are splendidly exhibited at all the rapidly growing ends of the long bones.

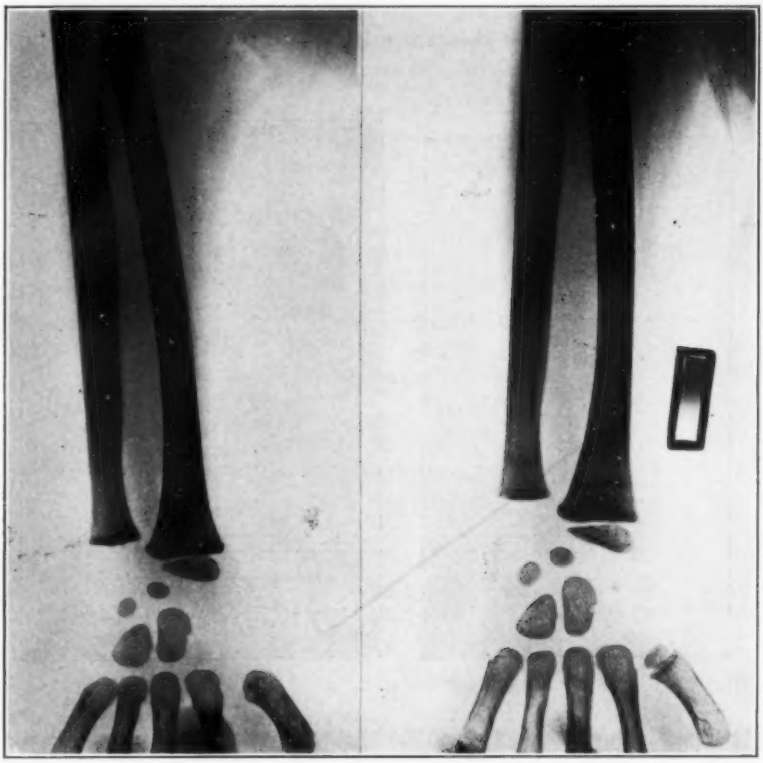
Superimposition must be nearly perfect, if the shadow caused by lead is to have sharp definition. We have repeatedly observed great variations in the opacity in a given band, it being much greater in one part, for example, the outer than the inner where the superimposition was poor on account of curvature of the cartilage-shaft junction.

Kasahara and Hiroshima have described the lead zones as though they occurred indiscriminately at the ends of the long bones of the arms and legs, the ends of the ribs, the metacarpal bones and phalanges, the peripheries of the ossification centers of the tarsus and carpus, the nuclei of ossification of the epiphyses and along the peripheries of the flat bones, such as the ilium and scapula. One might infer from their paper that in lead poisoning zones of increased density developed alike at all growing endochondral centers. Such is not our experience. In a great majority of the cases of lead poisoning the strata in the bone produced by lead either cannot be seen at all in the slowly growing parts or else they give rise to shadows which cannot be distinguished with certainty from those which are normal at the cartilage-shaft junctions. Whether the shadows produced by lead are present or not in the more slowly growing parts of the skeleton, we are certain that the shadows in those localities are not important so far as the recognition of lead poisoning is concerned. The only parts of the skeleton in which lead zone formation becomes characteristic are at the points of rapid growth. In one of our cases the ilium was beautifully marked by a double band. In our severe cases of lead poisoning in young children we have been able to find lines in the metacarpal bones and phalanges and at the slow growing ends of the long bones of the extremities, after our attention had been directed to the existence of lead poisoning through the discovery of the broad dense formations at the fast growing cartilage-shaft junctions of the arms and legs. One of Caffey's illustrations gives a beautiful example of ring-shaped shadows in the carpal bones and nuclei of ossification of the epiphyses.

We now call attention to a curious phenomenon seen in the bones of children whose exposure to lead poisoning had stopped completely before the time when the film was taken.

At the sites of rapid growth in such cases one often sees two zones of increased density, the one at a variable distance from the end of the shaft, the other at the end. When we first observed this phenomenon, we thought there must have been a previous episode of poisoning, to account for the zone separated from the end of the shaft, and a present episode to account for the one at the end. After the most careful investigations for evidence of recurrence in the lead poisoning had failed, however, we were compelled to explain the phenomenon in the

following way. The older zone, the one away from the end of the shaft, was incurred during the period of the ingestion or inhalation of the lead. The zone at the extreme end of the shaft was the result of the continued redeposition of the lead liberated from the lead depots in various parts of the skeleton. Lead is deposited in all those parts of the skeleton which are in process of growth at the time that the poisoning occurs. In the course of physiologic resorption of bone lead is con-

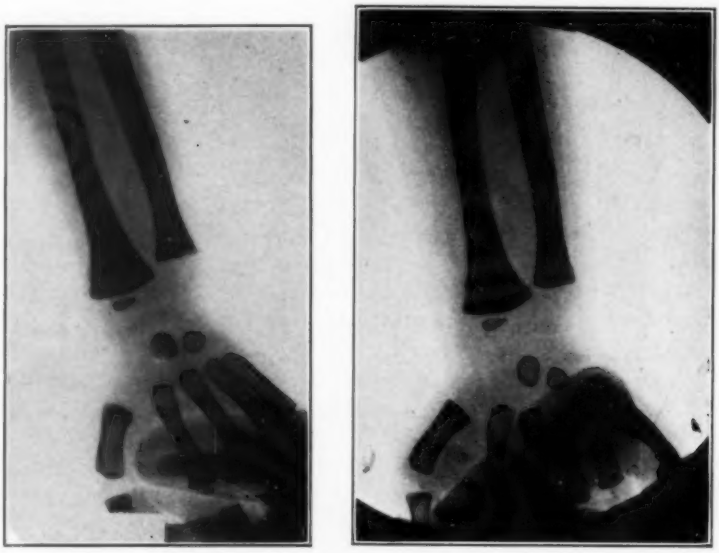


Left. Right.

Fig. 2.—J. J. (H. L. 70434), aged four years, had eaten paint for some time. An x-ray film of the bones of the forearm (left-hand film) showed snowy white bands about 1.5 millimeters wide at the lower ends of both radius and ulna. If doubt had existed that these were lead bands, the doubt would have been removed by the x-ray film taken nine months later (right-hand film) of the same bones, which showed these bands as beautiful typical lead zones now situated *above* the lower ends, 9 millimeters above in the case of the radius and 10 millimeters above in the case of the ulna. In the interval of nine months, in other words, the radius and ulna grew at their lower ends 9 millimeters and 10 millimeters respectively. Moreover, in the right-hand film additional snowy white bands broader than those in the first picture (left-hand film) are present *at* the ends. The right-hand film presents, therefore, a beautiful example of the "double zone phenomenon."

tinually liberated into the circulation. The matrix of the cartilage bordering on the shaft has a great affinity for lime salts and, as shown by experiments on the young rat with diets deficient in calcium, will

take lime salts out of the blood at a lower solubility product than newly forming bone is able to do. This fact is inferred from the observation that in the case of the young rat on the low calcium diet the provisional zone of calcification of the cartilage may be completely calcified while the recently formed bone on the surfaces of the trabeculae of the shaft shows no evidence of lime salt deposition whatsoever. Lead is so closely related to calcium in its reactions with phosphorus, that the intercellular substance of the growing cartilage must keep taking the lead out of the circulation exactly as it does the calcium. The lead, like the calcium, must, therefore, keep describing a circle. Part of the lead liberated from



Left. Right.

Fig. 3.—B. McC. (H. L. 61457), aged two years, gnawed paint for 1 year prior to the first x-ray picture (left). The "double zone phenomenon" is well shown in both pictures, better in the radius than in the ulna, as usual. The two shadows in the radius are 3.5 millimeters apart. It is noteworthy that the older of the two shadows, the upper one, is much the fainter. Moreover, its trabecular composition and the indefiniteness of outline are well shown. The lower shadow in the x-ray film was snowy white, completely homogeneous, and its outline sharp. The structure of the bone between the two shadows is denser than in the normal part of the shaft.

The right-hand picture was taken one month after the first during which time the paint-eating had entirely stopped. Nevertheless, the shadow at the lower end of the radius has increased a full millimeter in breadth.

the tissues is excreted, but the rest is taken out of the circulation by the growing bone, particularly by the matrix substance of the growing cartilage, and becomes fixed in the latter in sufficient quantity to cause a lead zone to continue to form at the end of the shaft for a long time after the lead has ceased to enter the body. Aub, Fairhall, Minot and Resnikoff[16] have advanced and demonstrated this hypothesis. They

have shown that in lead poisoning the lead is distributed throughout the organism and, since the skeleton is the only tissue to retain permanently any significant amount of lead, an ever increasing percentage of the total absorbed lead comes to be stored in the bones. After absorption has ceased, this selective localization of lead becomes practically complete. Aub and his associates showed that a slow excretion of lead takes place for long periods of time after the entrance of lead into the body has ended, proving that a liberation of lead from its places of storage occurs more or less continuously.

When the end of the shaft is marked by two zones, as just recorded, the bone between the two will usually be found to cast a more dense shadow than the rest of the shaft. In many cases the intervening bone exhibits transverse line formation. If the poisoning occurred a long time before the film was taken and growth has been rapid, the space separating the two zones will be considerable, e.g., 6 millimeters. If, on the other hand, the interval between the period of ingestion or inhalation of lead and the taking of the x-ray film has been brief, the two zones may be separated by a break of not more than a line. It is not uncommon to find that the lead band at the end of the bone appears as if sharply divided into two parts by a linear zone of decreased density. Beautiful illustrations of this phenomenon will be found in the paper by Caffey.*

A proof of the double zone phenomenon is beautifully supplied by the increase in the breadth of the dense band at the end of the bone for some time after the poisoning has ceased. For example, in the case of B. McC. (H. L. 61457), aged two years, paint had been eaten for one year prior to the first x-ray film. Though the paint eating had entirely stopped for one month previous to the time when the second x-ray picture was taken, the second picture showed that the dense terminal zone had broadened by as much as a millimeter.

The observation that the lead zone at the end of the shaft may continue to broaden after the poisoning has ended was first called to our attention by Dr. Bela Schick and Dr. Emile Stoloff and their associates at Mt. Sinai Hospital, New York City.

The fact that lead is being continually given off by the skeleton from its points of storage for a long time after the poisoning has come to an end explains why the lead zone in the substance of the shaft does not possess sharp outline. With the cessation of the poisoning, the poisoning does not end, so to speak, but gradually becomes less and less as more and more of the lead is finally excreted from the body. Hunter and Aub[17] have demonstrated experimentally that lead may be thrown out, in large quantities from the skeleton as the result of the administration of certain acid salts and of parathy-

*See pages 968 and 969, Case 1.

roid hormone both of which cause an acceleration of the physiologic disintegration of the skeleton. Such experiments indicate that in the normal person the liberation of lead from the skeleton must be subject to variation. The irregular liberations of lead into the circulation may be responsible for some of the differences in the density of the shadows in the lead zone and may even explain some of the lines of increased density. Certainly one obtains the impression from the study of x-ray films in many cases in which the lead poisoning seems to have been continuous that the initial effect on the skeleton was greater than subsequent effects, because the older part of the lead zone, that which must have been formed in the initial stage, is far more dense than the remainder. The explanation is not clear.

In our previous article we pointed out that on theoretical grounds zones of increased density from lead could not be expected in the adult, because lead formations could develop only in those parts of the skeleton in process of growth. A study of the x-ray films in our series of children aged from one to thirteen years indicates that after the fifth year the development of lead zones at the growing ends of the long bones is not so definite a phenomenon as in the younger child and is, therefore, not so reliable an aid in diagnosis. In a number of instances in children six or more years of age the terminal zone of increased density was so narrow, that we were totally at a loss to know whether to interpret it as a lead zone or merely as an exaggeration of the normal condition such as may be produced by viosterol. In some older children, however, terminal bands of not more than 1.5 millimeters in breadth were so snowy white as to indicate that the underlying condition was a pathologic phenomenon, in all probability due to lead.

In a number of cases in which we could not be certain whether to regard the terminal band of increased density as due to lead, time came to our rescue. As new bone formed, a characteristic lead zone was left behind.

Of course for a lead zone to develop time is required. We have seen beautiful lead zones in the middle ribs, 2 to 3 millimeters in breadth, in an infant whose period of lead poisoning was two months. Probably the poisoning must last at least a month to produce a well-defined formation in the bone. At the time of acute poisoning, it is not reasonable to expect the shadow in the bone. If the acute poisoning is survived, a shadow may, perhaps, slowly make its appearance.

Since lead is deposited at all points in the bone where active growth is in progress, one might expect that in lead poisoning characteristic linear shadows would form in those parts of the cortex where growth is active or that the shafts as a whole would acquire an increased density. We have not been able, however, to find alterations in density about

which we could feel certain in any parts of the bone other than those bordering on the endochondral growth centers. Kasahara and Hiroshima have described the occurrence of characteristic shadows in the tables of the skull. If shadows develop in those regions, they have only an academic interest.

We know that with time the lead zones diminish in thickness to not much more than lines and at the same time become fainter. Finally, they are with difficulty distinguishable and disappear. The duration of the shadows depends on such factors as the initial size and density of the band and the rapidity with which resorptive processes take place in the bone. In the case of W. M. (H. L. 79255), aged seven years, the extremely sharp snowy white terminal band, 1.5 millimeters in thickness at the lower end of the radius was just discernible in the x-ray film taken nine months later, 5 millimeters above the end. A corresponding shadow was not visible at the lower end of the ulna. Our data bearing on the subject of the disappearance of the lead zones in the x-ray films are too few to permit any conclusion. We are under the impression, however, that the lead zones usually become so reduced in the course of a year that they no longer give well-defined shadows. Great variations occur in the length of time that transverse lines persist in the bones and, doubtless, in the duration of lead formations in different children, depending on differences in age (growth and resorption of bone) and in states of health and nutrition.

THE PATHOLOGIC CONDITION RESPONSIBLE FOR THE SHADOWS

In order to make clear the pathologic condition in the bones which causes the shadows, it is necessary to review briefly the growth of normal bone, because in the knowledge of the normal depends the understanding of the deviation which occurs in lead poisoning. Growth in length in the long bones depends primarily on the growth activity of the epiphyseal cartilage. The epiphyseal cartilage keeps producing new material in the form of new cartilage as long as growth lasts, and, as fast as formed, the shaft keeps converting this new material into bone and thereby increasing in length. The forces of the shaft can produce growth in thickness, but so far as growth in length is concerned, the shaft is mendicant to the cartilage, as is so well illustrated in chondrodystrophy.

As the generating part of the proliferative cartilage produces new cartilage for conversion into bone, the cells in the new cartilage form, roughly speaking, into columns. These columns lie close together singly or in groups and, though somewhat irregular, are disposed in the long axis of the bone. The columns of cartilage cells lie completely embedded in the matrix substance of the cartilage, so that they are separated from each other by thin films of matrix substance. If the columns of cartilage

cells in the proliferative cartilage were suddenly to disappear, the matrix substance left behind would be filled with holes lying in the longitudinal axis of the shaft. Thus the matrix substance minus its cartilage cell columns might be compared to a section of honeycomb. The matrix substance deprived of its cells, however, would lack entirely the perfect geometric formations of the honeycomb, since the cavities in its interstices would vary much in size and shape, the walls would vary in thickness and apertures would exist in the walls where the latter were deficient and the columns of cartilage cells had joined and run together.

The agents for the conversion of the newly formed cartilage into shaft (bone) are the blood-filled capillaries and their accompanying connective tissue cells which on contact with the matrix substance or with bone rapidly change into osteoblasts. The way in which these agents convert the material furnished by the cartilage into bone is as follows: Lime salts deposit in the part of the cartilage which is in contact with the shaft. They do not deposit in the cartilage cells but in the matrix substance which envelopes and separates the cartilage cell columns from each other. As they deposit in the matrix substance they convert it into a hard material. The capillaries, impelled by some chemotactic influence, grow against the cartilage cell columns (not against the calcified intercellular substance), destroying the cells of the columns and, as they do so, creating holes in the calcified matrix. Into these holes the capillaries with their accompanying osteoblastic cells continue to grow; the osteoblasts settle on the exposed walls and begin to spread over the surfaces thin cellular networks of bone. As the result of the settlement and growth of the osteoblasts on the shell-like walls or partitions of calcified matrix and the production on them of bone, the development of the bony trabeculae begins. The calcified matrix substance becomes the core of the trabecula, as the osteoblasts cover it over with one layer after another of bone. In the cancellous tissue of the growing bone at some distance from the cartilage-shaft junction, the cartilage cores of the trabeculae can be identified by their property of staining purple with hematoxylin. But we are anticipating.

The phenomena just described are those which occur in the cartilage as the result of the action upon it of the capillaries and osteoblasts. But close by, in the shaft bordering on the cartilage, another phenomenon takes place which from the standpoint of bone formation is of equal importance with its predecessors. In the present study an understanding of this is of especial importance because it supplies the key to the abnormal condition brought to pass at the growing end of the bone by lead. The phenomenon is the destruction of the framework of calcified matrix in its greater part close in the wake

of the advancing surface of capillaries and osteoblasts. Although no one knows exactly how the destruction of calcified matrix is brought to pass, the agents seem to be the same as those which cause new bone to form, namely, the osteoblasts with their attendant capillaries. The destruction of the calcified matrix, at or close to the cartilage-shaft border, is an even one and is certainly not haphazard. Probably it is determined by the requirements of stress and strain. Those parts of the structure of calcified matrix, which are destroyed, are those not needed and those parts of the structure which survive and become heavily encased by osteoblastic bone, are the ones lying in the lines of force. The trabeculae which emerge from the destruction are, relatively speaking, few. They form an open-work structure which might be compared to the steel work in a tower. The spaces between the trabeculae become filled with marrow. The importance in the present discussion, of the knowledge that under normal conditions the greater part of the dense structure of calcified matrix furnished by the cartilage to the shaft is removed almost immediately after its calcification and invasion by the capillaries lies in the fact that in lead poisoning the matrix substance which becomes permeated with lead as well as calcium in its greater part is not destroyed, but persists. The persistence of this framework of matrix filled with the salts of lead and calcium phosphate is the essential lesion in the bone in lead poisoning and is responsible for the characteristic shadows in the x-ray film.

But before describing the actual pathologic condition in the bone, it is necessary to make a slight digression. Bone produced by apposition and, also, membranous bone, stains pink with eosin in hematoxylin-eosin preparations. It shows under the microscope a definite cellular and fibrillar structure. On the other hand, the cartilaginous matrix, when containing phosphate salts, stains the intense blue or purple of hematoxylin. Moreover, it is entirely homogeneous, when looked at under the microscope, and, since it is a dead substance, being a cellular product, it does not exhibit any cellular structure. By means of the ordinary hematoxylin-eosin stains, therefore, one can differentiate with great ease the matrix substance of cartilage from osteoblastic bone. In lead poisoning the same differentiation holds. The matrix substance filled with lead as well as calcium phosphate stains an intense blue and exhibits a homogeneous structure; the bone stains pink and presents bone corpuscles and fibrils separated by cement substance.

After this preliminary discussion we now describe the actual pathologic condition in the bone which results from lead poisoning. On gross examination of the bone cut longitudinally, the yellow line which normally marks the junction of epiphysis and diaphysis is broader and more conspicuous than usual. It is sharply demarcated on the cartilage

side and does not show the irregularities which are frequently so striking in cases of congenital syphilis. The characteristic abnormality is most conspicuous when the histological preparation, which has been partially decalcified in Müller's fluid or formic acid and stained with hematoxylin and eosin, is examined. If a histologic preparation, taken through the cartilage-shaft junction longitudinally and prepared in the way mentioned, is held to the light, one can see that the end of the shaft for a

Fig. 4.—E. U. (H. Ł. 67267), aged twenty-one months, gnawed paint for two months, to within ten days of death. The x-ray film of ribs, taken after death, shows beautiful terminal bands which in the x-ray film were snowy white, homogeneous and sharp.

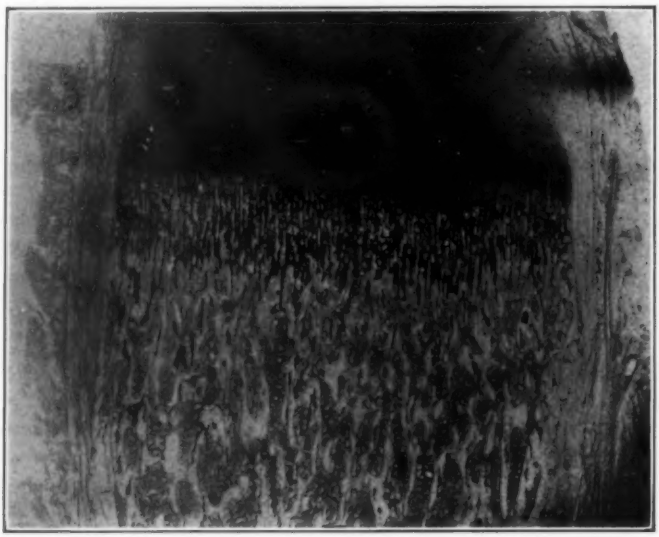


Fig. 5.—A low power view (15×) of the rib in Fig. 4, stained with hematoxylin and eosin in order to differentiate between the trabeculae of the matrix substance of the cartilage and the trabeculae of bone. Above is the resting cartilage, then the zone of proliferative cartilage, then the trabeculae formed almost entirely of matrix substance (in the photograph appearing as vertical black lines) and below the trabeculae of bone, separated from each other by marrow. The trabeculae of bone appear colorless; in the histologic preparation they are stained pink. The zone filled with the trabeculae of cartilaginous matrix appears black on account of the dark blue stain, taken by the latter. The trabeculae of matrix substance are thickly placed and present an orderly parallel arrangement in the long axis of the bone. They are filled with lead and calcium phosphate and are responsible for the shadow across the end of the bone seen in Fig. 4. The trabeculae of bone show the dark staining cores of cartilaginous matrix substance which were the original nuclei of origin.

distance perhaps of several millimeters takes a dark blue stain and that the structure in the blue area is unusually dense. The blue color is much deeper, more purplish, than the blue of the cartilage and is in sharp contrast to the normal part of the shaft, which appears pink. On placing the histologic preparation, such as described above, under the microscope, the essential features of the pathologic condition seem to be as follows. Between the cartilage which has an entirely normal appearance, on the one side, and the normal appearing part of the shaft on the other, there lies a thick framework of trabeculae which stains deep blue. One can see that it is this framework of trabeculae which is responsible for the dark blue appearance of the terminal portion of the shaft, seen so well when the histologic preparation was held to the light. These dark blue staining trabeculae have a parallel arrangement in the longitudinal axis of the bone and present a remarkably regular and well-ordered appearance, showing that the general plan of growth had been left undisturbed. The trabeculae are so close to their neighbors as to be separated by not much more than their own breadth. On following the blue staining trabeculae upward they can be seen to be continuous with the deposits of lime salts in the provisional zone of calcification of the cartilage. This observation makes the essential feature in the pathologic condition produced by lead clear; namely, that, the deep blue staining trabeculae represent merely cartilaginous matrix framework, in this case filled with lead as well as calcium phosphate, which the cartilage has left in its wake in the process of growth and which has not been destroyed. In the histologic preparation, which offers for study merely a single sheet of tissue so thin as to represent practically a single plane, the blue staining framework with its parallel trabeculae lying in the longitudinal axis of the bones might be compared to rather thickly placed perpendicular bars in an iron gate, but if the framework were seen in its three dimensions, it could be likened to the stems at the bottom of a hedge. We have chosen this simile because the trabeculae are not perfectly straight. Moreover, there is branching between them. It is true that *some* destruction of this framework has taken place, because in the older parts the interstices between the columns are wider than in the more recently formed parts close to the cartilage. But in general the amount of destruction has been very little. Examination shows, also, that on the surface of these blue staining trabeculae of calcified and *leadified* cartilaginous intercellular substance new formation of bone has occurred, for here and there, particularly in the older portions (those farthest from the cartilage-shaft junctions) margins of pink staining bone with their characteristic bone corpuscles can be seen. But just as the destruction of the matrix substance has been slight, so the new bone formation on the surfaces of the trabeculae of matrix substance has been slight.

Though the persistence of the network of cartilaginous matrix is by far the most striking phenomenon produced by lead in the skeleton, there is another phenomenon which is also noteworthy. The interstices of the network of trabeculae are filled with giant cells of all shapes and sizes. In no other condition in the bone (tumors, of course, excepted) have we ever seen so many giant cells or giant cells of such dimensions. In general they are more numerous and larger in the

Fig. 6.—Low power (12×) magnification of the histologic preparation of the rib of D. G. (H. L. 69978), aged two years, who was known to have eaten paint. On admission the child was thought by the surgeons to have a brain tumor. Injection with air having failed to reveal evidence of one, the child was transferred to the pediatric service, where the diagnosis of lead meningitis and encephalitis was made through the discovery of the characteristic lead bands in the x-ray films. The end of the shaft appears black from the dense mass of trabeculae of cartilaginous matrix. The trabeculae further back in the shaft appear colorless (in the histologic preparation pink) because they are composed of bone. The dense thicket of trabeculae of dark blue staining matrix substance, filled with lead and calcium, was responsible for the well-defined, thin, terminal band of increased density in the x-ray film of the ribs, which is not reproduced here.

Fig. 7.—A higher power (60×) view of the histologic preparation seen in Fig. 6. The giant cells can be clearly seen. Also, it is now apparent that the trabeculae of cartilaginous substance which appear black in the photograph are coated in places with thin coverings of bone. The thin coverings of bone appear in the picture as colorless borders along the black matrix substance. The bone formation is much greater in the older portions, i.e. in the parts furthest removed from the cartilage-shaft border, which latter is visible at the top of the picture. (See opposite page.)

Fig. 8.—Still higher power (260×) view of the histologic preparation seen in Fig. 6, included in order to show the huge giant cells interspersed in the spaces between the trabeculae of matrix substance in the lead zone. The films of bone which have formed on the surfaces of the matrix substance can be seen in several places and in one of them (the lower right-hand corner) the bone corpuscles and the lining osteoblasts are clearly depicted. (See opposite page.)

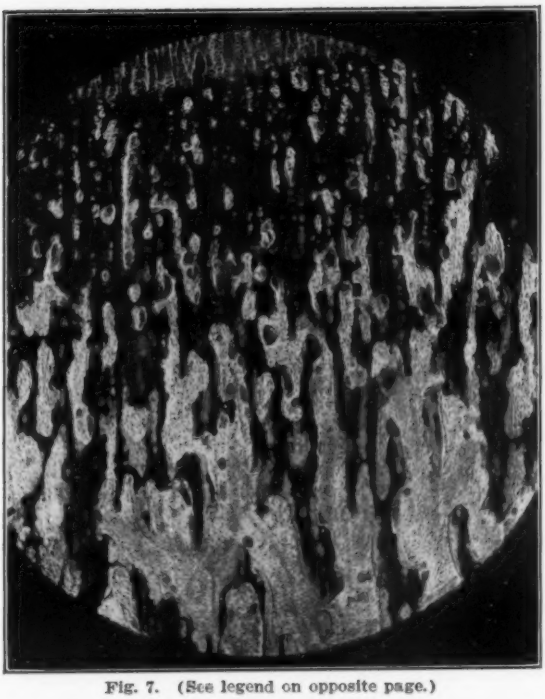


Fig. 7. (See legend on opposite page.)

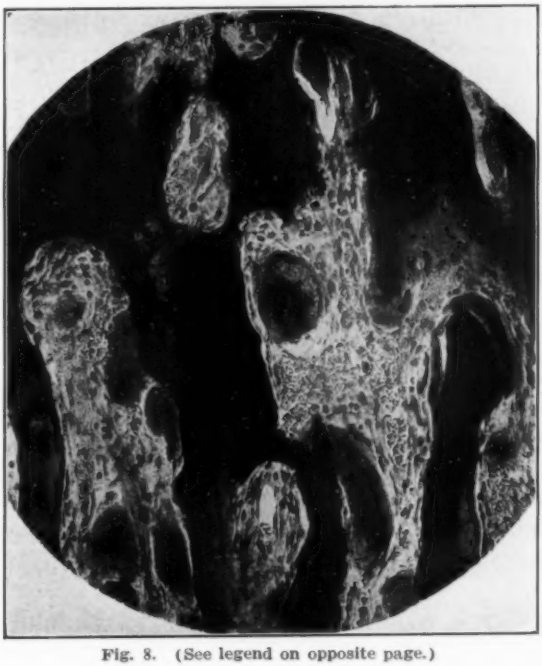


Fig. 8. (See legend on opposite page.)

older parts of the network, but they are also present in the newly forming parts close to the cartilage-shaft border. Some are round, some oval; most are irregular and many have long drawn out processes which entwine the trabeculae. Some are small and appear to have only two or three nuclei, others are huge and have hundreds. In some the nuclei are well preserved and show one or two nucleoli, resembling the nuclei of the osteoblasts; in other instances the nuclei appear degenerated and hardly take the hematoxylin stain. In many of the giant cells the nuclei are shaped and arranged like connective tissue and appear as a great mass or tuft of osteoblasts might appear, if its cells suddenly fused. In some instances the nuclei are situated in the center of the cell, in others they lie to one side or they may be aggregated in several parts of the cell or scattered about. The cell bodies of many of the giant cells appear degenerated, being filled with refractile bodies; in other cases they have a smooth homogeneous appearance almost indistinguishable from bone. In general the giant cells lie along the trabeculae, but in many instances they are situated in the spaces between. Perhaps the giant cells which do not appear to be in contact with the trabeculae were actually in contact in planes above or below that of the section. They seem to be particularly fond of the gaps in the trabecular formations and appear as though growing through from one space into another. They are especially likely to be found in corners and crevices and to twine around trabeculae, one anastomosing with another by means of long protoplasmic arms and appearing to envelop a trabecula after the fashion of a vine. Dr. Warren Lewis who has examined the sections thinks that in some of the giant cells foreign bodies are present. We cannot make any definite inferences concerning the origin of the giant cells or their purpose. No obvious relationship seems to exist between them and areas of bone destruction. It seems most probable that they represent fusions of osteoblastic cells. They may well be stimulated by foreign bodies.

It is as difficult to say whether or not the osteoblasts are more numerous or less numerous than in normal bone as to say whether or not swallows are more or less numerous in one season than in another. There seem to be many osteoblasts. But as already indicated the amount of new bone formation, which is easier to estimate seems to be less than normal. In the spaces of the trabecular framework can be seen blood vessels filled with blood, connective tissue-like cells, osteoblastic cells and huge giant cells already mentioned. Mingled with the above here and there are also marrow cells singly or in groups, but the marrow is not abundant until the normal bone is reached. There it presents the usual appearance.

The two striking features seen in the histologic preparations are the

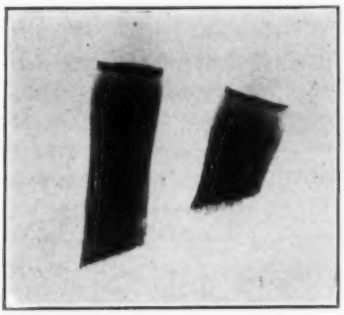


Fig. 9.—K. H. (H. L. No. 64117), aged two years, died of pneumonia and pneumococcus peritonitis. The bands in the ribs, 5 mm. above the ends, were accidental discoveries after death and made us suspect that previously the child had suffered from lead poisoning. Spectroscopic examination of the dense zones showed that lead was present in them.

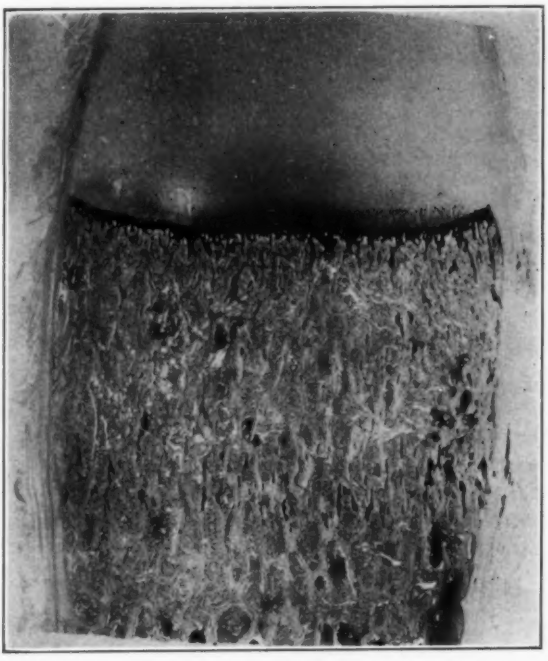


Fig. 10.—Histologic preparation of the rib shown in Fig. 9. The remnants of the lead zone which is responsible for the band seen in the x-ray film are visible in the microphotograph as a transverse formation 1.5 cm. broad and 6.5 cm. below the cartilage-shaft junction. The telltale feature is the cores of cartilaginous intercellular substance which stain black and are themselves the remnants of the original lead zone, which was probably very heavy at the time of its formation. The cores of matrix substance still show the parallel arrangement in the longitudinal axis of the shaft which is so characteristic a feature of the lead formations freshly developing at the cartilage-shaft junction.

persistence of the framework of cartilaginous intercellular substance of the cartilage which the chemical studies of others have shown to be filled with lead as well as calcium, and the huge giant cells just described. We have already stated that we could not explain the presence of the giant cells. We do not understand, either, why the framework of intercellular substance of the cartilage persists. At one time we considered the possibility that the lead in the trabeculae poisoned the cells which might be concerned in their disintegration. In congenital syphilis and in scurvy, as will be discussed later, the preservation of the framework of calcified cartilaginous matrix is associated with, and probably depends on, a cessation of osteoblastic activity. We judge that in lead poisoning the activity of the osteoblasts close to the cartilage-shaft junction is not great and perhaps the preservation of the calcified and *leadified* matrix substance formations in lead poisoning depends on a lowered osteoblastic activity. Without being able to explain why, then, it seems probable that the preservation of the framework of matrix substance is connected in some way with its content of lead which makes it less easy to destroy, or else it depends on some inhibitory action of lead on the cells which under ordinary circumstances destroy it.

In one case we have had the opportunity of studying the lead zone in a rib which lay 5 millimeters from the cartilage-shaft junction and must, therefore, have been formed some months previously.

The formation consisted of trabeculae which were larger and more thickly placed than elsewhere and contained thick cores of cartilaginous matrix substance. Obviously, in the course of time the matrix substance had been in very large part removed by the destroying forces of the shaft and the parts which remained had become heavily encased in bone. On spectroscopic study of this area, lead was found to be present. The case shows how with time the lead formation left farther and farther behind by cartilage as growth progresses is gradually destroyed by those forces which keep causing old bone to disintegrate.

CAUSE OF THE SHADOWS

In a previous communication* Park, Jackson and Kajdi expressed themselves as follows in regard to the cause of the shadows produced by lead: "So far as it is possible to be influenced toward any conclusion from our two cases, we should suppose that the lead modified endochondral ossification in such a way that the trabeculae formed under the cartilage a much more dense thicket than normally, and that these formations of densely packed trabeculae were the cause of the band-like shadows. On the other hand, we admit the probability that lead itself

*Rf. 2, Page 13.

was in the trabeculae, and that it may have been partly responsible for the shadows. In any event, an anatomic explanation for the shadows was present in the only two cases which permitted of histologic study." Vogt[3] explained the opacity as being due solely to the lead. The truth seems to be as follows. The lead is the chief and probably the essential cause of the shadow, if the analysis of Aub in Vogt's case and the analyses in Caffey's case hold for others. In Vogt's case Aub found that in the dense areas at the ends of the bones the lead per gram of bone was 0.527 and the calcium 0.124 grams. The ratio of lead to calcium was greater than 4 to 1. In Caffey's case 1 gram of dry bone taken from the dense zone yielded 0.7 grams of lead. The atomic absorption coefficient for x-rays varies approximately as the fourth power of the atomic number for the element concerned. The atomic number of lead is 82 and of calcium 20. Accordingly the coefficient will be about 280 times as great for lead as for calcium. From values obtained by actual measurement, however, the ratio of the absorption coefficient of lead to calcium is about 40 in the region of 0.4 ängstrom units, the region occupied by the ordinary x-ray.* Organic bone casts no more shadow than muscle or connective tissue, as is so well illustrated in rickets. It is, of course, the lime salts in organic bone which are responsible for the shadows cast by bone. In other words, it is because of the extraordinary property of organic bone to adsorb the salts of calcium and phosphorus that bone appears differently in x-ray films from other tissues. The trabeculae in the normal bone are the containers for the calcium and in lead poisoning are the containers for both lead and calcium. If they were not there, no zone of density would exist because there would be no tissue which could hold the lead. The trabeculae are the anatomical units responsible for the shadow and on the abnormal persistence of the great mass of trabeculae of cartilaginous intercellular substance the existence of the shadow and its breadth and finer structure in lead poisoning all depend.

CONFUSING SHADOWS FROM CAUSES OTHER THAN LEAD

As a preliminary to the discussion of this subject it should be appreciated that the lower ends of the radius and ulna, the lower end of the femur and both ends of the tibia and fibula of children two years or more old normally often show dense terminal outlines which are similar to the terminal zones of increased density seen in slight degrees of lead poisoning.

In children treated with viosterol the shadows at the ends of the shafts of the bones just mentioned are apt to be unusually intense. Dr.

*This statement was kindly supplied by Isador Lævin, Ph.D., of the Department of Chemistry, Johns Hopkins University.

Shelling has kindly permitted us to study some of the histological preparations in his series of children who died from various diseases while undergoing treatment with viosterol. The condition found at the cartilage-shaft junction, when studied under the microscope, seemed merely an exaggeration of the normal. The deposition in the cartilage (the provisional zone of calcification) was unusually heavy and the trabeculae of calcified intercellular substance lying immediately under the cartilage were perhaps more numerous and somewhat longer than usual. The lime

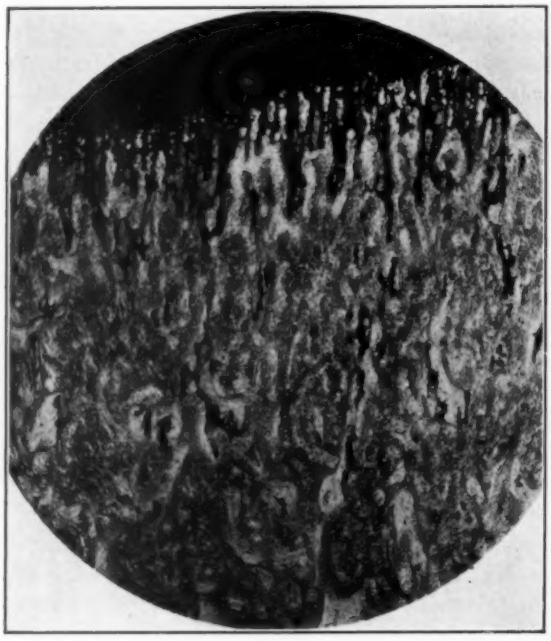


Fig. 11.—L. C. (H. L. 70399), aged eighteen months, dying of tuberculosis. For some time previously the child had been receiving viosteral in large doses. The condition at the cartilage-shaft junction as seen in the histologic preparation, (magnification 60×) is a beautiful example of the normal. But the calcification in the cartilage appears unusually heavy and the trabeculae of calcified cartilaginous substance with their actively forming investments of bone seem longer and somewhat thicker than usual. The calcium deposits in the cartilage and the hedge of newly forming trabeculae sticking out of the undersurface of the cartilage are the cause of the shadow in the normal bone with or without previous viosterol treatment.

salts in the cartilage and the subjacent trabeculae were responsible for the shadow in these children treated with viosterol as they are in the untreated child. Treatment with viosterol by no means always causes the end of the shaft to develop a zone of increased opacity. In some of Dr. Shelling's cases in which viosterol treatment had been continued for a long time the ends of the shaft did not present any unusual appearance.

In our experience the shadow produced by the viosterol is seen only at the cartilage-shaft border. It never persists, to become buried in the shaft substance, as do the shadows produced by lead and phosphorus or the transverse lines which appear when growth is suddenly arrested.

Transverse lines marking arrests in growth have already been referred to and are abundantly discussed in the papers previously mentioned. When transverse lines are in the process of formation at the cartilage-shaft border of the bone, the end of the shaft appears to have an unusually bright outline. When they become submerged in the substance of the shaft as the result of the formation of new bone beyond, they always appear as lines, even at the rapidly growing ends of the long bones. Often they alternate with zones of rarefaction and appear in series, one above the other and exactly parallel. They are similar to the transverse zones of increased density caused by lead in that they can be seen in the x-ray film to be made up of the shadows of the trabeculae. In transverse line formation the microscope shows that at the site of the line the trabeculae show cross-branching and the cause of the transverse line is the summation of the shadows of the trabeculae and their cross branches. The transverse line formation is composed of bone and is, therefore, totally different from the formation induced by lead which is composed of cartilaginous intercellular substance. In the latter formations cross-branching is not a feature. The lines produced by arrests in growth are sharply outlined in the x-ray film in contrast to the zones of increased density produced by lead, and, moreover, lack the breadth of the latter, i.e., they appear as lines and do not merit the term, zones. Allusion has been made to the fact that the lead formations at the slowly growing ends of long bones are linear.

Phosphorus bands are totally different from the lead formations. In our very limited experience with phosphorus bands the band is much more dense than the corresponding formation produced by lead; indeed it is so dense that it appears homogeneous. Moreover, its borders, both on the proximal and, provided it has been left behind in the process of growth, on the distal side, are sharp. Phosphorus bands situated at the extreme ends of the shaft, denoting from their situation that the phosphorus poisoning was in progress, might be indistinguishable from bands produced by lead in similar situations. But so soon as the lead formation has been distanced by the growing ends of the shaft, its obvious trabecular composition and indefinite outline at once distinguish it from the bands produced by phosphorus. Under the microscope the two formations are as different as black and white. As already pointed out, the lead formation consists in a dense thicket of trabeculae of cartilaginous intercellular substance which is filled with the salts of lead

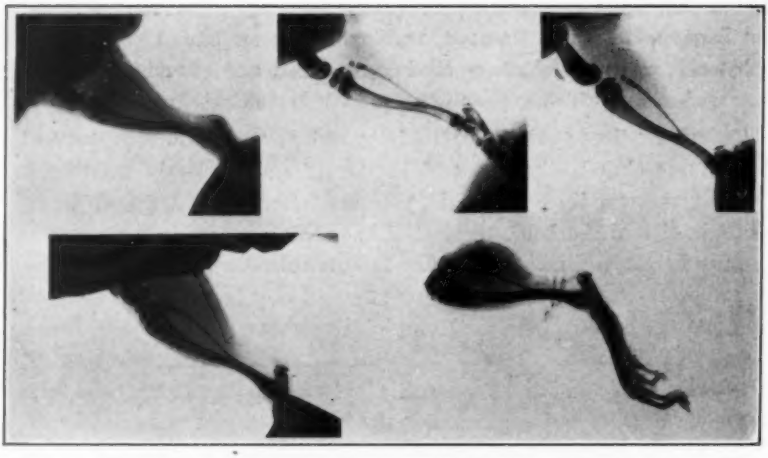


Fig. 12.—Elementary phosphorus bands experimentally produced in the rat: upper row reading from left to right, the tibia before the beginning of the phosphorus-containing diet; after 1 week on the diet; 2 weeks; 3 weeks; 4 weeks. Note that the phosphorus band which was snow white in the original film steadily increases in breadth.

Fig. 13.—The histologic preparation of the tibia seen in Fig. 12, low power magnification. Above is the center of ossification; below is the shaft. Separating the two is the dark band of proliferative cartilage. The upper part of the shaft is filled with a thick network of trabeculae composed of bone, (not cartilaginous intercellular substance). The trabeculae of bone appear colorless (pink in the hematoxylin-eosin preparation). (The dark areas between are the marrow). One can make out the bone corpuscles in the trabeculae which are no larger than dots. It is this dense mass of trabeculae formed as the result of the heightened osteoblastic activity which gives the dense shadow characteristic of elementary phosphorus.

and calcium phosphate. These trabeculae show scant envelopments of bone. In the formations produced by elementary phosphorus the characteristic feature is a thick network of bone. The elementary phosphorus must stimulate enormously osteoblastic activity with the result that under the microscope the field of the transverse band is filled with a veritable meshwork of trabeculae of bone interlacing in every direction. One can even see mitoses in the osteoblasts, a phenomenon which we have not observed in any other condition. The pathological basis for the shadow in poisoning with elementary phosphorus is, therefore, totally different from that seen in lead poisoning.

Both scurvy and congenital syphilis can produce dense shadows at the ends of growing bones. We are fully aware that the shadows are rarely, if ever, confounded with those produced by lead. We include in our consideration, however, the shadows produced in scurvy and congenital syphilis because the anatomical substratum of the shadows in the two diseases is very similar to that produced in lead poisoning. In both scurvy and congenital syphilis the dense shadow at the ends of the shaft is produced by dense aggregations of trabeculae composed entirely of calcified cartilaginous intercellular substance. In both diseases new bone formation at the cartilage-shaft junction is in abeyance or has ceased entirely. Thus little or no new bone forms on the surfaces of the trabeculae of calcified cartilaginous substance and the latter, persisting in great quantities, through superimposition cause the dense shadow in the x-ray film. The formations of calcified intercellular substance which give rise to the distinctive shadows in scurvy and congenital syphilis are quite irregular, and the irregularities are clearly depicted in the x-ray film. In the lead formations the normal architecture of the bone is beautifully preserved. As already pointed out the shadows in lead poisoning are caused in greater part by the lead itself, whereas in syphilis and scurvy the dense shadows are produced by the calcium. In both congenital syphilis and scurvy other distinctive features of the respective diseases are present in the bone and in the x-ray film, but we shall not discuss them here. Healing rickets is another condition in which the heavy shadows at the extreme ends of the shaft are caused by deposits of lime salts in cartilaginous intercellular substance (not in bone). In rickets, scurvy and congenital syphilis the shadows are seen only at the ends of the bone. With increase in the growth they always disappear and never give rise to shadows at a distance from the end of the shaft. In scurvy, congenital syphilis, and especially in rickets transverse line formation due to suddenly arrested growth is a very common phenomenon. It bears no relationship, however, to the formation of the dense shadows at the extreme ends of the bone just described.

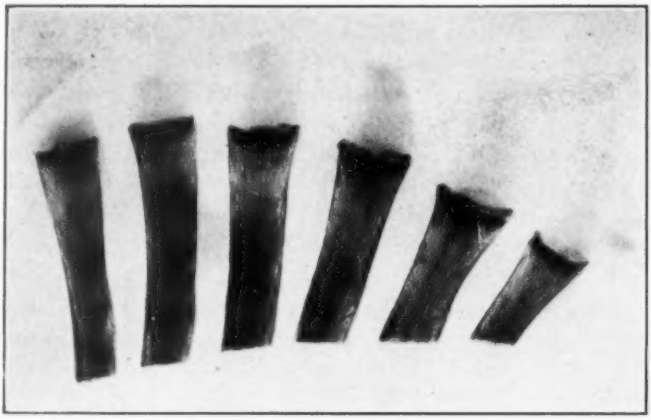


Fig. 14.—A. S. (H. L. 71652), aged ten months, entered the hospital with scurvy and died of so-called alimentary intoxication. The x-ray films of the ribs taken post-mortem show beautifully the dense terminal zones which appeared white and the extreme rarefaction characteristic of the disease.

Fig. 15. (See opposite page.)

Vogt[4] states "Recently we obtained films of a child who was being treated for congenital syphilis by the intramuscular injection of a bismuth compound. These showed quite dense zones at the ends of the long bones. We intend to make further observations, however, before we ascribe any definite significance to these observations." We are able to confirm Vogt's surmise as the result of one of our own observations. M.K. (H. L. 78476), aged 3 months, was a healthy baby who was given

Fig. 16.—Higher power view of Fig. 15, showing above, the proliferative cartilage, below, the trabeculae formed entirely of calcified intercellular substance without a trace of bone.

viosterol, first in 15 drop doses daily for 5 weeks, later in 30 drop doses for 6 weeks. She received in addition 8 grams of bismuth salicylate daily for the last 4 weeks of the viosterol treatment; i.e., for the 4 weeks im-

Fig. 15.—A low power view of the histologic preparation of one of the ribs in Fig. 14, showing the cause of the dense terminal shadows. The cause is the thick mass of trabeculae composed entirely of the calcified matrix substance of the cartilage. The trabeculae appear black (the blue stain of hematoxylin) in contrast to the slender irregularly running trabeculae of bone in the body of the shaft which appear gray (pink in the hematoxylin-eosin preparation). In scurvy osteoblastic activity is diminished or suspended. The preservation from destruction of the mass of trabeculae of calcified intercellular substance, which keeps accumulating at the end of the shaft with continued growth of the cartilage is probably connected with the abolition of osteoblastic activity. In scurvy the trabeculae of matrix substance cast the dense shadow as the result of their calcium content; in lead poisoning the cause of the shadow cast by the trabeculae of matrix substance is chiefly the contained lead.

mediately preceding the x-ray studies. The x-ray film shows a beautiful transverse formation extending across the lower ends of both radius and ulna which we believe is due to bismuth. It is possible, of course, that the viosterol shared in the production of the zone of increased density

Fig. 17.—Lower end of femur of stillborn child with congenital syphilis showing the dense terminal zone characteristic of that disease. As often happens in congenital syphilis the cartilage-shaft junction in the film is marked by numerous points and irregularities; i.e., the irregularities are toward the cartilage.

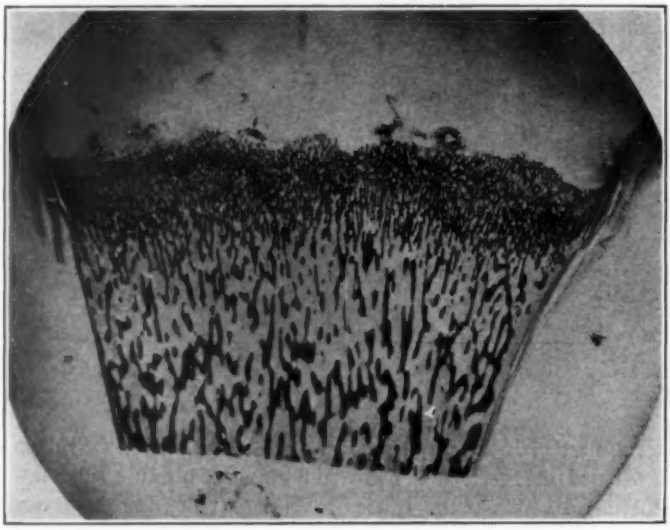


Fig. 18.—Low power view of the histologic preparation taken from Fig. 17. The dense shadow seen in the film corresponds to the dense zone of trabeculae of calcified cartilaginous matrix substance occupying in the photograph the terminal 2 centimeters of the shaft. The trabeculae take the dark blue stain (black in the photograph) because they are composed entirely of matrix substance. The trabeculae of bone below the band zone stain gray, though they show beautifully the dark staining central cores of cartilaginous matrix on the surfaces of which the osteoblasts originally settled and began their activities. The irregularities at the cartilage-shaft border correspond to those seen in the x-ray film. They are explained on the ground that in congenital syphilis the proliferative cartilage becomes calcified more rapidly where its nutrient vessels, the cartilage canals, join the shaft than elsewhere. The angles, elevations and irregularities in the outline of the end of the shaft are, then, merely outgrowths from the end of the shaft at the sites of the cartilage canals. The explanation of this phenomenon in congenital syphilis is new.

but we have not seen such zones from viosterol alone. Another example of a beautiful "bismuth formation" has been furnished by Dr. Frederick Tisdall of Toronto. Theoretically, bismuth *should* cause zones of increased density to develop in bones.

THE RELATIVE MERITS OF FIVE CARDINAL SIGNS IN LEAD POISONING

When one suspects lead poisoning in a child, one searches for a history of contact and examines for certain well-known manifestations, but in addition one investigates or should investigate for the presence or absence of five special signs of lead poisoning; namely, anemia, stippling of the red blood cells, the lead line on the gums, the characteristic shadows in the x-ray films of the bones and the presence of lead in the circulating blood, as determined by spectroscopic examination. We now undertake to make clear the relative merits of these signs in the diagnosis of lead poisoning.

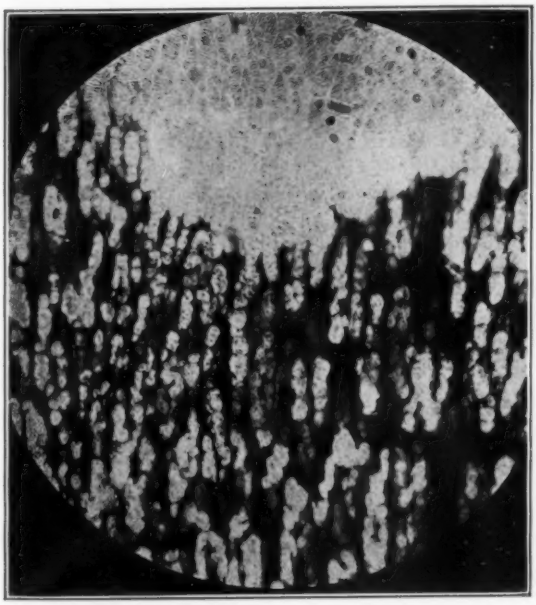


Fig. 19.—A yet higher power view of Fig. 18, showing that the trabeculae of calcified matrix are entirely lacking in bone formation in active congenital syphilis. They stain dark blue and fail to show anywhere borders of bone. At the top of the photograph can be seen the proliferative cartilage. As in scurvy the mass of trabeculae of cartilaginous substance casts its dense shadow in the x-ray film by virtue of the calcium content of the trabeculae.

Probably the least important of the signs mentioned is anemia. In our series of cases a moderately low hemoglobin was noted in the majority, but only rarely was the anemia of a severe degree. Twice in

uncomplicated lead poisoning was the hemoglobin below 45 per cent and only in one-sixth of our series did it fall to less than 50 per cent. When present the anemia is secondary in type and presents no characteristics which would make it pathognomonic of lead poisoning. In a few of the acute cases no anemia was present.

Basophilic stippling of the red blood cells is a sign of much more importance than anemia, but it, too, is not entirely trustworthy, as in many severe secondary anemias stippled cells are found in the blood. Stippling is often an intermittent phenomenon in lead poisoning. In

Fig. 20.—M. K. (H. L. 78476), aged four months, who received bismuth salicylate two and one-half months prior to the time when the x-ray film was taken. The main bismuth line is seen 3.5 mm. above the lower end of the radius. Two additional lines are present which may be bismuth lines or may represent merely disturbances in growth.

one of our most severe cases of lead poisoning, well proved by clinical signs and chemical determinations, daily examination of blood smears was made. Only once was our search rewarded, and on that particular day many stippled cells were found. The pouring out of stippled cells by the bone marrow is the result of some unknown stimulus, apparently not an even one. In our cases whose blood was examined, 70 per cent had basophilic stippling. It is noteworthy that in 30 per cent no stippling could be found. Lead poisoning should be considered, when stippled cells are found, and their presence is strong corroborative evi-

dence of poisoning. One weakness of stippling as a sign of lead poisoning is the ease with which it may be overlooked.

Lead line is not so satisfactory a sign in infants and young children as it is in adults. Thirty-five per cent of our patients showed it. When it is typical, it proves that lead is, or recently has been, circulating in the blood. The diagnosis is established, if symptoms of lead poisoning are present. Often this sign is difficult of recognition because of the failure of young children to cooperate in the examination, and in some cases the limited extent of the line. In one child it was found only on the inner gums above an upper incisor and bicuspid. Adequate light and magnification are almost essential in the discovery of the lead line,

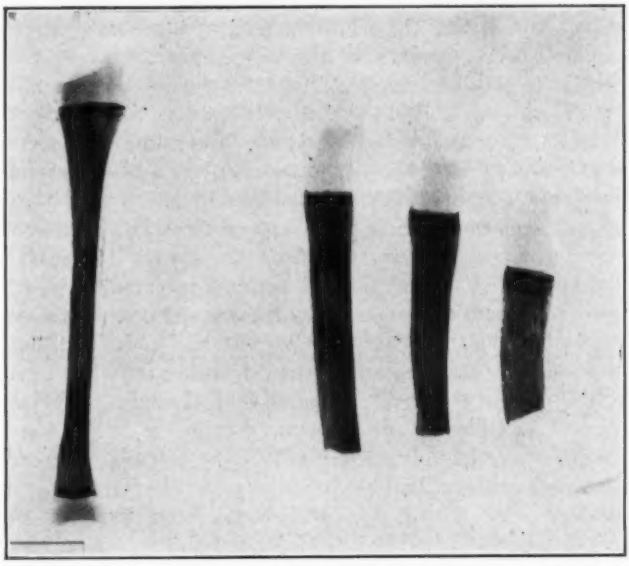


Fig. 21.—E. J. H., dying in the Hospital for Sick Children, Toronto, at the age of three and one-half months. During the second month of life the child had received bismuth salicylate. The bismuth lines are beautifully depicted. Doubtless viosterol which the child had received daily, favors the absorption of the bismuth and intensifies the bismuth formation in the bone. The line is probably to be attributed to bismuth supplemented by viosterol rather than to bismuth alone.

(We are indebted to Dr. Frederick Tisdall for permission to reproduce this picture.)

and we have found the electric otoscope particularly suitable for the inspection of the gum margin. In fact, we do not think an adequate examination has been made unless this method is employed and the line specifically looked for. Confusion is often caused by the dark pigmentation normally found in the mouths of so many negro children. Careful inspection may be necessary to distinguish it from the lead line which is usually narrower, more stippled in appearance and nearer the gum margin. Many children, therefore, with outspoken lead poisoning fail to show the line, and it will not usually be found unless specifically looked for.

If the lead line may be spoken of as a hidden sign of lead poisoning, the shadow in the bone caused by lead is a bright signal which cannot be missed. On two different occasions young children who had been operated upon for brain tumor with the discovery that brain tumor was not present, were sent to the Harriet Lane Home for diagnosis. The x-ray pictures of the bones of the arms and legs showed the characteristic shadows of lead poisoning. In a case of our own, a child aged 4, suspected of having a brain tumor, was observed in the wards for a month. The possibility of tuberculoma was considered and the chest was x-rayed, in order to see whether evidences of tuberculosis could be found. In the x-ray plate the heavy shadows at the ends of the humeri were noted and furnished a clue to the diagnosis of lead poisoning. Further investigation proved that the condition was the meningo-encephalitis of lead poisoning. The shadows in the x-ray films of the bones are of value chiefly by way of suggestion that the condition from which the child is suffering may be lead poisoning. They may be so characteristic, however, as to make lead poisoning almost a certainty. Characteristic features of the lead zone when it lies away from the end of the shaft are its trabecular composition and its lack of sharp definition. The "double zone" phenomenon is highly suggestive; i.e., a characteristic trabeculated shadow at a distance from the end of the shaft and a shadow of metallic quality at the end with the intervening bone having an opaque quality and often crossed by transverse lines. Dense terminal bands themselves may most strongly suggest lead poisoning, but dense bands at the ends of the shafts are caused by other conditions. A dense band at the end of the shaft indicates that the lead poisoning is in progress; one imbedded in the shaft away from the end means merely that lead poisoning has occurred previously. The time of occurrence can be gauged quite easily by a knowledge of the rate of growth of the particular bone. The double band should mean that lead poisoning has occurred previously and that lead derived either from an exogenous source or from the depots in the patient's own tissues is circulating in the blood at the time. Many times we have seen the band in the substance of the bone in cases in which the poisoning had stopped entirely months or even a year before.

The spectroscopic test for the presence of lead in the circulating blood is so recent a development and our experience with it is so limited, that a proper evaluation of its usefulness is not possible.[18] A negative spectroscopic test of the blood for lead proves that lead is not circulating and indicates, therefore, that lead poisoning is not occurring. A negative test is certainly of the greatest usefulness. A well-marked positive test means that lead is circulating in the blood and indicates either that lead poisoning is still going on or has occurred recently. The difficulty in interpreting the spectroscopic test in the present state of our ignorance is its delicacy. We do not know, for example, if garage workers and others

exposed to lead in their daily occupations may not give positive spectroscopic tests, even though not suffering in any respect from lead poisoning. We do not know for how long a time after the poisoning is over the spectroscope will continue to yield a positive test for lead in the blood. By means of the spectroscope Shipley, Scott and Blumberg found lead circulating in the blood in patients whose inhalations of lead had ceased one month previously. If the child shows symptoms of lead poisoning, a positive spectroscopic test for lead in the blood is of the greatest value. A negative test has been of the greatest possible value in our hands on a number of occasions by withdrawing lead poisoning entirely from the field of possibility. Probably lead must reach a certain concentration in the blood before it gives rise to symptoms. Below that concentration it will deposit in the bones and probably it can give rise to the lead line. With the aid of the spectroscope it will probably be possible to determine quantitatively the amount of lead in the blood and to obtain data in that way which will enable an accurate estimate of its significance in a given case. As our knowledge increases, the test will come to be by far the most reliable and useful of all the tests for lead poisoning.

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ALIMENTARY INTOXICATION IN INFANTS. ACID-BASE EQUILIBRIUM WITH THE USE OF CONTINUOUS INTRAVENOUS THERAPY (PRELIMINARY REPORT)*

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UNCERTAINTY still prevails concerning the etiology, the pathologic physiology, and the methods of treatment of so-called alimentary intoxication. The multiplicity of names given to the condition in pediatric literature reflects this uncertainty. Alimentary intoxication, toxicosis, anhydremia, severe diarrhea, acute diarrhea with dehydration and acidosis, cholera infantum, are but a few of the names used to designate this clinical syndrome. All efforts to find a specific etiologic factor have been in vain. The most that can be said at present is that the clinical picture may accompany a variety of enteral and parenteral infections including acute otitis media, mastoiditis, pneumonia, dysentery, burns, pyodermias, pyelitis and streptococcic sore throats. In some instances the severity of the clinical picture is out of proportion to the amount of infection.

Whatever may be its basic pathologic condition four primary factors seem to make up the clinical picture, namely, infection, dehydration, toxicosis and acidosis. However, the correction of one or even all of these does not necessarily correct the condition. Thus, Howland and Marriott,[18] Hartmann[14] and Schloss and Stetson[33] have restored acid base equilibrium without affecting mortality. Marriott[25] attempted to combat infection with equally discouraging results. It is possible to correct the dehydration to the point of a positive water balance, yet fatal termination ensues. It must, therefore, be concluded that much remains to be learned about the true nature of this condition.

In the latest edition of their classic treatise *Des Kindes Ernährung*, Czerny and Keller,[4] quoting the senior author, state as follows:

"Schon vor 30 Jahren hat Czerny den Standpunkt vertreten, das die alimentaren Toxikosen aufhören oder nur sehr selten zu beobachten sein werden, wenn die Kinder gesund in den Sommer hereinkommen, wenn jede kleinste Ernährungsstörung sorgfältig behandelt und ausgeglichen wird und wenn die Bevölkerung soweit erzogen wird, das sie schon wegen geringer Ernährungsstörungen des Kindes

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This paper belongs to the Czerny Festschrift group.

sachverständige ärztliche Hilfe aufsucht und nicht erst, wenn sich schwere Krankheitserscheinungen zeigen. . . ." Der gefürchtete Sommergipfel der Säuglingssterblichkeit ist verschwunden, die Sterblichkeit ist im Winter jetzt bei uns höher als im Sommer. Diese Erfahrungen bestätigen die Richtigkeit unserer Anschauungen von der Bedeuting der prophylaktischen Behandlung der Säuglinge und beweisen, das wir in der Ernährungstherapie der Säuglige grosse Fortschritte erreicht haben. Das ist um so erfreulicher, als wir zugeben müssen, das wir in der Behandlung der katastrophalen Erscheinungen der alimentären Toxikose im Laufe der letzten Dezennien nicht wesentlich weiter gekommen sind."*

Undoubtedly the prompt recognition of alimentary intoxication and equally prompt and thorough treatment of infants with this condition is responsible in large part for the reduction in mortality. The excellent general condition of these children at the onset of the disease has also had a favorable effect.

Examination of more recent studies in therapy makes one feel, in spite of Czerny's pessimism, that something has been accomplished in the treatment of alimentary intoxication. Table IV shows the mortality rates of more recent reports from several institutions. Early recognition of the disease, followed by prompt treatment leading to the restoration of kidney function,[34] the restoration of normal chemical equilibrium in the blood, the elimination of the material burden which the gastrointestinal tract must bear, and the establishment of adequate drainage from accessible suppurating foci, have all contributed to the reduction in mortality. The relative importance of each individual measure is hard to estimate. Schloss[34] stressed the early restoration of kidney functions. Marriott[24] pointed out the rôle played by infection of the ears, mastoids and accessory nasal sinuses. Hartmann,[14] Hoag and Marples[15] and Powers[29] have emphasized the importance of combating anhydremia. Monrad[26] shows the necessity for prolonged periods of starvation and large amounts of fluid and offers statistical evidence in support of these views. Powers[29] believes that the systematic application of all of these measures has brought about the reduced mortality in his more recently treated cases.

The administration of parenteral fluids is generally considered among the most important procedures in treating alimentary intoxication. The intermittent use of glucose intravenously immediately

*For thirty years Czerny has maintained the attitude that alimentary toxicoses will disappear or will be met with only seldom if the children enter the summer season in a healthy state; when the mildest disturbance of nutrition is carefully treated and corrected and when the people are enlightened to appeal for competent medical care at the slightest appearance of nutritional disease in children and not to wait until severe manifestations appear . . . . The authors further state that the much feared summer maximum in infant mortality (from alimentary intoxication) has disappeared. The death rate is now higher in winter than in summer. The authors conclude that experience confirms the correctness of their point of view concerning the significance of the prophylactic management of infants and proves that we have made great progress in the nutritional therapy of infancy. "This fact, they state, must be very gratifying in view of the fact that one must admit that we have made no progress in the management of the catastrophic manifestations of alimentary toxicosis during the last decennium."

preceded by saline given by hypodermoclysis, together with a fixed dietary regime has proved its value.[15] More recently Karelitz and Schick[19] claimed to have shown the advantage of the continuous intravenous drip over previous methods of fluid administration. The striking reduction in mortality reported by these authors, led us to seek confirmation of their claims and to determine, if possible, the superiority of this method of treatment through a clinical study of the patient and a quantitative study of the blood. We used this method in conjunction with other accepted adjuncts of present-day therapy (starvation, treatment of infection).

In spite of the striking symptoms presented by a typical case of alimentary intoxication, we feel that many cases have been grouped in this class that, obviously, are only moderately severe gastroenteric disturbances, a fact which explains in part the marked variation in mortality in different clinics. We used the following criteria in choosing our cases: (1) history of vomiting and diarrhea of varying severity; (2) presence of clinical dehydration as manifested by diminished tissue turgor, dryness of mucous membranes, sunken eyeballs and depressed fontanelle; (3) the presence of intoxication as shown by nervous irritability, and later clouding of the sensorium often to the point of coma; (4) the presence of "air hunger" indicative of acidosis; (5) frequent presence of circulatory failure (ashen-gray, cold skin, cyanosis); (6) presence of infection; (7) chemical changes in the blood which we shall mention in a discussion of the chemical data.

PROCEDURE

Procedure.—As soon as the child was admitted to the hospital, it was examined by one of us, and if deemed a suitable subject for study, blood was taken for chemical examination. The blood was usually drawn from the external jugular vein and was then placed under oil and allowed to clot. The patient was then placed on a specially constructed mattress for the simultaneous and separate collection of urine and stool.[16] A vein in the anticubital fossa was dissected out and the continuous intravenous started. A Murphy tube was used to control the rate of flow, which was maintained at 6 to 10 drops per minute. Five per cent glucose in normal saline was used in every case. The total quantity varied from 600 to 1200 c.c. per day. Blood transfusions were not used as a routine procedure, but only when special indications presented themselves.

Blood for chemical examination was again drawn when the child first showed clinical improvement, and before discharge from the hospital. The constituents studied included total base, chloride, CO_2 combining power, total nitrogen, total protein, nonprotein nitrogen,

calcium and inorganic phosphorus. The refractive index was determined on every sample of serum. (See Table I.)

The child was given a period of complete starvation varying from twelve to twenty-four hours. The duration of this period was determined by the amount of vomiting and diarrhea. Following this the child was given small doses of 5 per cent glucose by mouth. This was increased very slowly. If there was definite diminution of toxicity and improvement in the diarrhea, formula was started after about twenty-four hours. We used reenforced protein milk in all cases.

The intravenous flow was maintained until diuresis was well established, dehydration corrected, and until toxicity had disappeared. With the above routine we found it possible in most cases to bring patients to a maintenance diet within three weeks after admission to the hospital.

We have made no attempt to combat the acidosis per se with sodium bicarbonate as advocated by Hartmann.

METHODS

Total base determined following the method of Van Slyke, Hiller and Berthelsen.[38]

CO_2 content determined according to Van Slyke and Neill[36] using the factors of Van Slyke and Sendroy.[37]

Chlorides determined on 0.2 c.c. of serum according to the Wilson and Ball's modification of the Van Slyke and Sendroy procedure except that 0.2 c.c. of 0.15 $AgNO_3$ was used and 0.01 K CNS.[35, 39]

Nonprotein nitrogen. Protein precipitate with 5 per cent trichloracetic acid aliquot of filtrate evaporated down with Kjeldahl digestion mixture followed by digestion.

Total protein. Howe's method was used for the determination of total protein.[17]

Nitrogen. The Parnas and Wagner modification of Pregl's micro-Kjeldahl method was used for the final determination of nitrogen.[28]

Cholesterol determined by Sackett's modification of Bloor method.[2]

Calcium was determined following the Kramer and Tisdall procedure.[22]

Inorganic phosphorus. The Fiske and Subarrow method was used for the determination of inorganic phosphorus.[5]

Sugar was determined by the Kramer-Gittleman modification of the Folin-Wu method.[6, 21]

Refractive index was determined by using a Zeiss dipping refractometer.

CASE REPORTS

CASE 1.—H. A., aged seven and one-half months, male, admitted Dec. 23, 1931, with temperature of 105° F. Severe diarrhea for three days before admission; no vomiting. Bilateral otitis media, purulent, acute, signs of rickets, semicomatose, extremely toxic, dehydrated. Diagnosis: bilateral otitis media, acute diarrhea with dehydration and intoxication. Blood serum total base and chlorides were normal, nonprotein nitrogen retention was marked. Child on continuous intravenous therapy for eight hours after admission. Remained anuric for fifteen hours. Improvement marked within forty-eight hours. As a result of treatment

there was a decrease in concentration of fixed base, dilution of blood serum as indicated by decreased protein concentration; considerable relative and slight absolute rise in chlorides. Disappearance of undetermined acids. At time of discharge, chloride was normal; protein concentration increased to normal level; nonprotein nitrogen which initially was very high decreased with reestablishment of diuresis. Child was placed on maintenance diet sixteen days after admission.

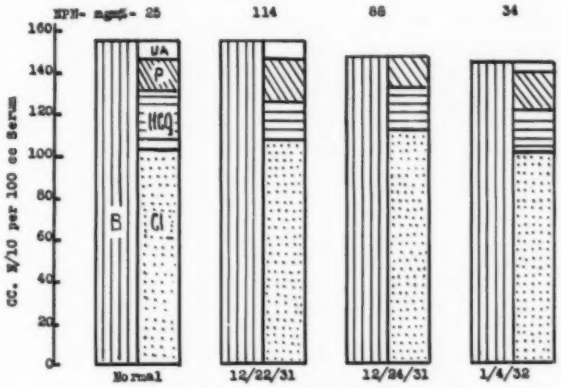

Fig. 1.—Case 1, treatment sixty-five hours.

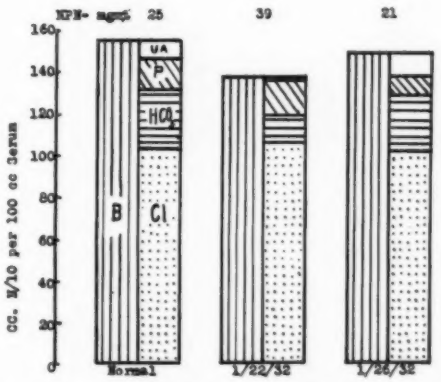

Fig. 2.—Case 2, continuous intravenous therapy one hundred two hours.

CASE 2.—S. B., aged four months. Male, admitted Jan. 22, 1932. Diarrhea one week prior to admission. Vomiting three days. Examination showed an upper respiratory infection, moderate dehydration, and definite toxicosis. Diagnosis: acute rhinopharyngitis, diarrhea with dehydration and intoxication. Blood serum total base was very low without proportionate drop in chlorides. Acidosis as evidenced by low bicarbonate and loss of fixed base. Continuous intravenous therapy instituted twenty-four hours after admission when marked toxicity and dehydration were manifest. Intravenous treatment for 102 hours produced marked dilution of blood serum as indicated by sharp drop in protein concentration which reduced oncotic

pressure of serum protein sufficiently to produce edema. Fixed base increased and chloride decreased slightly making possible an expansion of bicarbonate concentration. No blood transfusion was given. Diarrhea ceased after fifth day in the hospital. Patient recovered.

CASE 3.—A. D., aged two months. Male, admitted June 7, 1932. Vomiting and diarrhea three days. Otitis media, bilateral, purulent. Extremely dehydrated, ashen gray color to skin. Fontanelle depressed. Mucous membrane dry and cherry red in color. Diagnosis: acute otitis media, bilateral; diarrhea with dehydration and intoxication. Blood serum total base reduced, with marked absolute and relative increase of chloride concentration. Bicarbonate concentration was only 9 mm. Protein concentration was increased. Marked nonprotein nitrogen retention. Intravenous therapy instituted eighteen hours after admission and continued for forty-two hours. Began voiding six hours after onset of therapy. Blood serum total base remained at same level during intravenous therapy, but the chlorides and protein were reduced, thereby freeing fixed base for union with bicarbonate. Be-

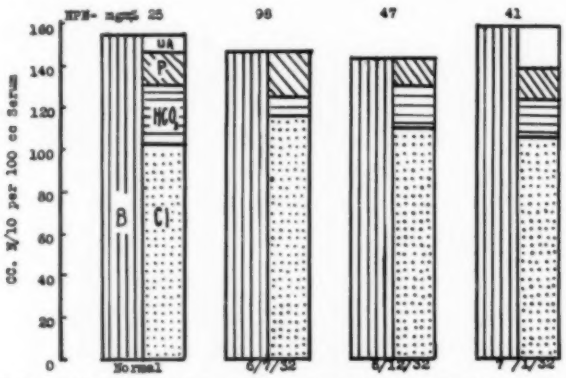

Fig. 3.—Case 3, continuous intravenous therapy forty-two hours.

fore discharge total base rose to a high normal. Chlorides and protein were normal. Undetermined acids presumably increased binding the extra fixed base. Nonprotein nitrogen became normal in three days. Child recovered; placed on maintenance diet eighteen days after admission to hospital.

CASE 4.—Aged four months, male, admitted July 28, 1932. Eight to ten watery stools daily for ten days. Vomiting two days, with a definite story of anuria of many hours' duration. Slight catarrhal otitis media, marked dehydration and intoxication; sensorium cloudy; fontanelle depressed. Diagnosis: acute otitis media, catarrhal; diarrhea with dehydration and intoxication. Intravenous therapy instituted upon admission and maintained for ninety hours. Complete starvation twenty-four hours; anuria six hours. Showed most marked reduction of fixed base with normal undetermined acids and protein concentration. Decrease in chlorides though marked was not sufficient to free enough base for union with bicarbonate. Intravenous therapy produced an increased concentration of fixed base to approximate the normal level. Restoration of chloride and sodium bicarbonate was effected in spite of a dilution of blood serum so great as to produce edema with markedly lowered serum protein concentration. Balance later reestablished at end of three

weeks by further increase in fixed base concentration and some decrease in undetermined acids permitting restoration of serum protein concentration. Edema developed in spite of marked diuresis which restored nonprotein nitrogen to the normal level.

Intravenous treatment was discontinued because of cardiovascular collapse, indicated by feeble pulse and cyanosis. Protein concentration at this point was 3.2 gm. per cent in 100 c.c. of serum, and there was marked edema of extremities.

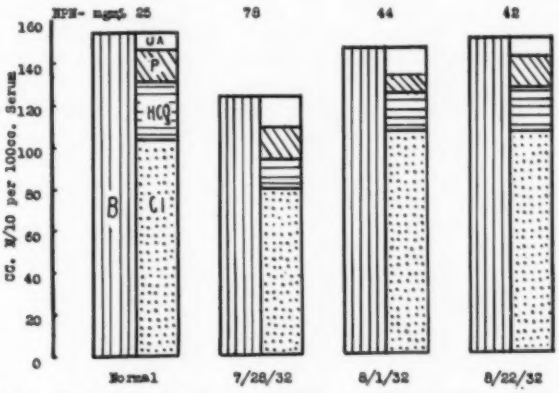

Fig. 4.—Case 4, continuous intravenous therapy ninety-two hours.

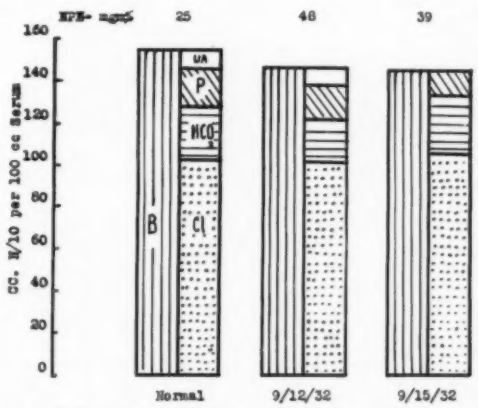

Fig. 5.—Case 5, continuous intravenous therapy fifty-four hours.

Child transfused immediately with 100 c.c. whole blood. There were several attacks similar to above during the succeeding few days. Child recovered and was placed on a maintenance diet eighteen days after admission to the hospital.

CASE 5.—S. B., aged five months. Admitted Sept. 12, 1932. Diarrhea two weeks' duration, vomiting one week. Temperature varying between 100 and 101° F. Markedly dehydrated infant, toxic, slightly depressed fontanelle. Diagnosis: acute rhinopharyngitis, otitis media, catarrhal, acute; diarrhea with dehydration and

intoxication. No acidosis. Continuous intravenous therapy instituted upon admission and maintained for fifty-four hours. Anuria for eight hours. In spite of administration of normal saline free from sodium bicarbonate, there was an increase in bicarbonate with no increase in chloride. Bicarbonate increase was at expense of protein and undetermined acids. Fixed base uninfluenced. Diarrhea checked within twenty-four hours after admission to hospital. Recovery prompt; maintenance diet in fifteen days.

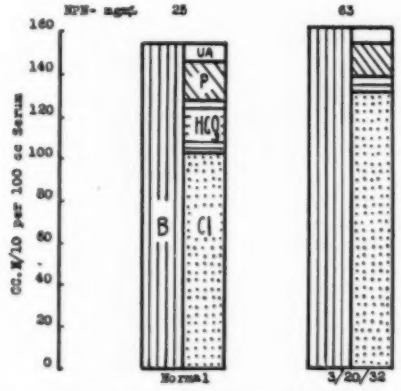

Fig. 6.—Case 6, continuous intravenous therapy thirty-six hours.

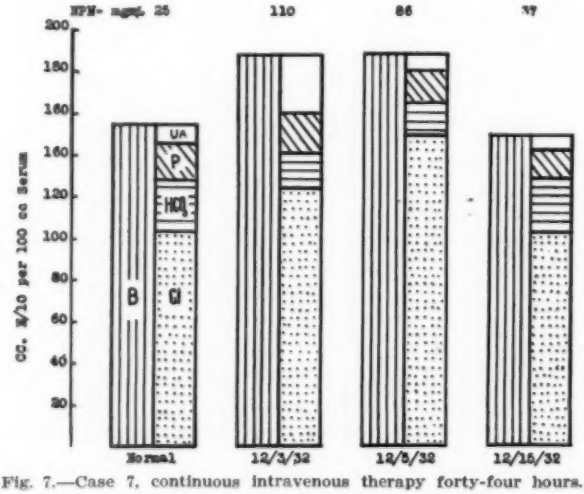

Fig. 7.—Case 7, continuous intravenous therapy forty-four hours.

Case 6.—P. F., aged two years, admitted March 19, 1932. Vomiting and diarrhea of two weeks' duration. Kussmaul breathing for at least two days before admission to the hospital. Stuporous. Marked dehydration with sunken fontanelle and eyes, marked skin lag and hyperpnea. Stools were positive for blood by guaiac test. Stool cultures were negative for dysentery bacillus. There was an extension of

chloride displacing bicarbonate, thereby producing a profound reduction in alkali reserve. Nonprotein nitrogen increased. Continuous intravenous therapy immediately on admission to hospital; transfusion ten hours later because of marked secondary anemia (Hb. -29 per cent). Patient died thirty-six hours after admission to hospital.

CASE 7.—H. M., aged seven months. Admitted Dec. 3, 1932. Vomiting and diarrhea three days prior to admission; fifteen to twenty stools a day. Temperature 101° to 102° F. Markedly toxic dehydrated child with sunken eyeballs, moderate skin lag, breathing slow and deep. Anterior fontanelle depressed, subcrepitant râles heard at right base posteriorly. Diagnosis: pneumonia, diarrhea with dehydration, intoxication and acidosis. Transfusion of 150 c.c. given immediately upon admission. Continuous intravenous drip for forty hours. Absolute starvation for eighteen hours with food starvation forty-eight hours. Anuria twenty-seven hours. Case showed highest fixed base concentration—188 mm. This permitted extension of chloride and undetermined acids. Protein concentration high, bicarbonate moderately re-

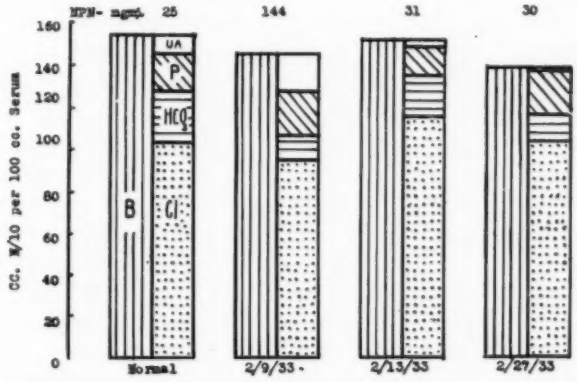

Fig. 8.—Case 8, continuous intravenous therapy eighty-two hours.

duced. Continuous intravenous therapy produced marked improvement in clinical condition, reflected in decreased nonprotein nitrogen and protein concentration. This improvement despite further increase in chloride and bicarbonate. After ten days almost complete recovery; chemical blood picture again normal. Maintenance diet restored in fourteen days.

CASE 8.—R. B., female, aged twenty-two months. Admitted Feb. 9, 1933. History of fever and cough five days before admission. Temperature 104° F. Many watery stools and repeated vomiting. Acutely ill child, breathing rapidly with an expiratory grunt. Skin had marked lag, eyes were sunken, and crepitant râles were heard at base of right lung. Left ear drum inflamed, not bulging. Blood culture positive for hemolytic streptococci. Diagnosis: pneumonia, otitis media, catarrhal acute left; septicemia, diarrhea with dehydration and intoxication. Treatment instituted nine hours after admission and continued for forty-eight hours. Because of sex, urinary collections were not possible. After intravenous therapy there was sharp reduction in nonprotein nitrogen, decrease in serum protein; increase in chloride at expense of protein and undetermined acids; decrease in latter sufficient to permit of expansion of bicarbonate and hence correction of acidosis.

We are unable to explain results obtained fourteen days later, shortly before discharge, protein increased to previously high level; chlorides had diminished. Nevertheless decrease in fixed base was such as to leave little room for undetermind acids and bicarbonate Reasons for this adjustment are not apparent from our data. It is possible that here too much treatment was given and fluid lost through urine with resultant change. Pneumonia and septicemia cleared up and child recovered. Discharged well four weeks after admission to hospital.

CASE 9.—M. L., aged two months, male, admitted Feb. 6, 1933. Diarrhea seven days. No vomiting. Temperature 102° F. for two weeks. Cough. Child hyperpneic, cyanotic, marked skin lag, depressed fontanelle, otitis media, catarrhal, acute, left. Diagnosis: alimentary intoxication, pneumonia, otitis media, catarrhal, acute. Continuous intravenous therapy started four days after admission and continued

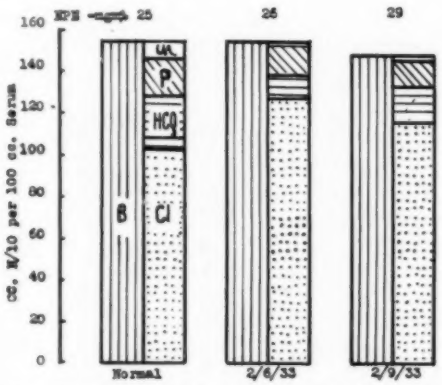

Fig. 9.—Case 9, continuous intravenous therapy forty-eight hours.

forty-eight hours. Blood serum showed high chloride which displaced bicarbonate. After three days chloride concentration dropped and bicarbonate increased but clinical condition became worse. Child died; no autopsy.

RESULTS AND DISCUSSION

Nine cases of alimentary intoxication were treated by the use of the continuous intravenous drip and starvation in an attempt to correct dehydration, to reestablish diuresis and to restore the chemical equilibrium of the blood serum. We aimed to study the inorganic equilibrium of the blood produced by the disease, as well as the concentration of such additional elements which past experience has shown to be significant. Our additional and perhaps more important purpose was to determine the effect of the administration of fluid in the form of saline glucose solution by the continuous intravenous method, both upon the clinical course of the disease and upon the inorganic equilibria in the serum.

Clinical Observations.—This is a preliminary report. We hope to report a larger series in a subsequent communication. Our clinical results were quite gratifying. Two of the nine patients treated died, giving a mortality of about 22 per cent. Table I gives a composite picture of both the clinical results and the chemical data. All of the cases presented the characteristic symptoms of alimentary intoxication, i.e., toxicity, dehydration, some clouding of the sensorium, often coma, and in five cases hyperpnea. Seven of the nine patients were seven months of age or under. All had evidence of infection, seven having otitis media while two suffered with pneumonia. One child who recovered had a positive blood culture (Streptococcus hemolyticus) on two occasions. A history of vomiting was present in all but two cases. All had severe diarrhea.

In all cases clinical improvement was noted in from twelve to forty-eight hours after treatment was instituted. In no case was significant clinical improvement noted until diuresis was established. The average length of time required to restore urinary flow was about ten hours, the longest period of anuria being twenty-seven hours, the shortest three hours. A point of interest was the apparently sedative action of the glucose saline solution upon the restlessness of the child. The duration of the intravenous therapy varied with each case, depending upon the clinical response of the patient. The average duration was about sixty-five hours, the longest period being one hundred and two consecutive hours, the shortest thirty-six hours. The periods of absolute and formula starvation depended upon the amount of vomiting and diarrhea and the degree of toxicity. In all cases we were able to resume a maintenance diet in less than three weeks. Two patients did not receive transfusions, three others for reasons other than the intoxication per se.

Chemical Data.—Our chemical data are particularly interesting, since we were able to control the fluid intake with a constant, slow, continuous drip, thus obviating the uncertain factors of variable absorption rates necessarily encountered when using hypodermoclysis, intraperitoneal injections or intermittent intravenous therapy. Furthermore, we were able to study the blood of each patient before and during active treatment, as well as during convalescence. Our findings in general confirm those of others working along similar lines but seem to differ in some respects.

The nonprotein nitrogen was studied on all cases. In general, we found a fairly close correlation between the nonprotein nitrogen concentration and the degree of toxicity. Our four severest cases (1, 3, 7, 8) had nonprotein nitrogen readings of 114, 98, 110 and

TABLE I

ALIMENTARY INTOXICATION

COMPOSITE CHART WITH CLINICAL AND LABORATORY DATA ON CASES STUDIED

CASE	DATE	AGE	DURATION OF SYMPTOMS	TOTAL BASE MM.	CHLORIDES MG. %	CHLORIDES MM.	CO_2 MG. %	CO_2 MM.	PROTEIN GM. %	PROTEIN MM.	U. A. MM.	NPN MG. %	CA. MG. %	P. MG. %	INTRAVENOUS TREATMENT HR.	INTRAVENOUS TREATMENT AMT.	TRANSFUSION	URINE 24 HR. OUTPUT	REMARKS
1	12/22/31	7½ mo.	3 days	155	381	107	42	18	8.78	21	9	114	9.2	2.4	65	880 c.c.		0-18 hr.	2 stools; otitis media bilateral; marked dehydration; comatose.
	12/23/31			147	397	112	48	20	7.07	17	0	88	9.2	2.4		1000 c.c.	150 c.c.	300 c.c.	10 stools; slight dehydration; alert.
	1/ 4/32			144	360	101	47	20	7.35	18	5	34	11.1	5.6					Normal; maintenance diet 16 days.
2	1/22/32	4 mo.	1 wk.	137	376	106	31	13	6.5	16	2	39			102	520 c.c.		180 c.c.	Moderate dehydration; drowsy; hyperpneic; otitis media catarrhal; 2 stools.
	1/26/32			148	363	102	62	26	3.88	9	11	21	8.7	3.2		800 c.c.		550 c.c.	Slight dehydration; alert; edema of prepuce, traumatic. No general edema.
3	6/ 7/32	2 mo.	2 days	146	413	116	21	9	8.74	21	0	98	10.2	5.4	42	575 c.c.	80 c.c.	225 c.c.	Moribund; anuria 6 hr.; marked dehydration; Kussmaul breathing; otitis media bil.
	6/13/32			143	390	110	47	20	4.83	12	1	47	8.2	3.1		765 c.c.		217 c.c.	Alert. Edematous.
	7/ 1/32			159	377	106	41	17	6.06	15	21	41		5.0					Recovered; maintenance diet 19 days.
4	7/28/32	4 mo.	10 days	123	279	79	34	14	6.25	15	15	78	9.9	6.5	92	1100 c.c.		212 c.c.	Stuporous; toxic; anuria 6 hr.; marked dehydration; otitis media bilateral.
	8/ 1/32			145	378	106	42	18	3.2	8	13	44		1.7		980 c.c.	100 c.c.	394 c.c.	Generalized edema; shock; cardiovascular collapse; transfused.
	8/22/32			149	371	105	49	21	6.3	15	8	42	9.6						Recovered; maintenance diet 18 days.
5	9/12/32	5 mo.	2 wk.	146	361	102	46	20	6.65	16	8	48	10.3	6.3	54	1200 c.c.		76 c.c.	Drowsy; hyperpneic; anuria 8 hr.; otitis media catarrhal; moderate dehydration.
	9/15/32			145	378	106	64	27	4.93	12	0	39	8.7	4.7		948 c.c.		324 c.c.	Recovered; maintenance diet 18 days.
6	3/19/32	2 yr.	2 wk.	162	468	132	16	7	6.74	16	7	63	9.6	2.3	36		100 c.c.	12 hr.— 90 c.c. 24 hr.—150 c.c.	Toxic; markedly dehydrated; ashen cyanosis; Kussmaul breathing; 4 watery stools; died.
7	12/ 3/32	7 mo.	3 days	188	442	124	40	17	8.0	19	28	110		10.1	44	700 c.c.	150 c.c.	0-27 hr.	Comatose; bronchopneumonia; cyanosis; marked dehydration; hyperpnea.
	12/ 5/32			189	533	150	36	15	5.75	15	10	86				750 c.c.		375 c.c.	Alert; edema face, eyelids and arms.
	12/15/32			149	365	103	58	25	5.95	14	7	37							Recovered; maintenance diet 14 days.
8	2/ 9/33	22 mo.	2 days	145	337	95	28	12	8.8	21	17	144			82	932 c.c.			Dehydrated; hyperpneic; Br. Pn.; otitis media; positive blood cul. hem. strept.
	2/13/33			152	413	116	46	19	5.88	14	3	31		2.7		1344 c.c.			Dehydration less.
	2/27/33			134	368	104	31	13	8.55	21	1	30		3.8					Recovered.
9	2/ 6/33	2 mo.	10 days	154	450	127	27	11	5.78	14	2	26		3.1	48			390 c.c.	Moderately dehydrated; toxic.
	2/ 9/33			147	409	115	41	17	5.15	13	2	29		2.8				615 c.c.	Dehydration marked; condition poor; died.

144 mg. per 100 c.c. of serum respectively. However, the last case, which almost approached the above four in severity, had a nonprotein nitrogen reading of only 26 mg. per 100 c.c. All patients showed a progressive drop in nonprotein nitrogen concentration with treatment and were discharged with normal readings. The nature of this high nitrogenous retention in many of these babies has been studied extensively in recent years, particularly by Schloss,[34] Marriott and others. Schloss concluded that the increased concentration of the blood alone does not account for the high readings, but that impaired kidney function is probably the basis for the retention. His conclusions were based upon kidney function tests (phthalein output and urea excretion), along with studies on blood concentration. Thirty-three of his forty-six cases had readings between 57 and 232 mg. per 100 c.c.* Marriott thought that the increase in nonprotein nitrogen was probably due to accelerated destruction of body protein, as well as to urinary retention. Atchley and Benedict[1] were able to produce marked nonprotein nitrogen retention in animals by ligating both ureters. Serum phosphates and sulphates were also tremendously increased. Haden and Orr[11] produced experimental dehydration in dogs by injecting 50 per cent sucrose intravenously. Four out of five of their animals showed terminal rises in nonprotein nitrogen and urea nitrogen. Hartmann[14] found increases in nonprotein nitrogen similar to ours. Hoag and Marples,[15] on the other hand, found a significant rise in only a few of their cases.

Inorganic phosphorus readings were usually low or within normal limits. Five of the 9 cases studied had readings of 3 mg. per 100 c.c., or less. Only one case (Case 7) had a reading of 10.1 mg. per cent. This child's nonprotein nitrogen was 110 mg. per 100 c.c. Though the chlorides were quite high in this child (442.2 mg. per cent), no acidosis existed, because total base was elevated in proportion to the chloride increase. Our results are at variance with the early work of Marriott and Howland,[18] and would seem to indicate that retention of phosphates plays but a minor rôle in the causation of acidosis in diarrhea. The data of Hoag and Marples[15] also fail to reveal any increase in inorganic phosphorus. In fact, the majority of their cases showed low initial readings which increased with treatment. This is especially significant in view of the presence of anuria in so many of their cases, as well as in our patients.

Our calcium determinations showed no characteristic changes.

Serum protein was determined both by the micro-Kjeldahl method

*The method employed by Schloss in determining nonprotein nitrogen concentration was different from the method employed by us.[36]

TABLE II

ALIMENTARY INTOXICATION. THE RELATION BETWEEN SERUM PROTEIN PERCENTAGE, FLUID INTAKE AND THE DEGREE OF CLINICAL DEHYDRATION

DATE	CASE NO.	REFRACTIVE INDEX	TOT. PROTEIN (MICRO-KJELDAHL) PER CENT	SERUM PROTEIN (CALCULATED FROM REFRACTIVE INDEX*) PER CENT	FLUID INTAKE IN 24 HR. C.C.	DEGREE OF DEHYDRATION
12/22/31	1	1.3524	8.78	8.76	880	Marked dehydration.
12/23/31		1.3496	7.07	7.31	1000	Slight dehydration.
1/ 4/32		1.3496	7.35	7.31		Absent.
1/20/32	2	1.3484	6.50	6.70	520	Moderate dehydration.
1/26/32		1.3419	3.88	3.35	800	Not dehydrated. Localized edema (traumatic) of prepuce.
6/ 7/32	3	1.3502	8.74	7.62	575	Marked dehydration.
6/13/32		1.3440	4.83	4.43	765	Edematous.
7/ 1/32		1.3460	6.06	5.46		None.
7/28/32	4	1.3471	6.25	6.03	1100	Markedly dehydrated.
8/ 1/32		1.3410	3.20	2.89	1080	Generalized edema.
8/22/32		1.3474	6.30	6.18		Normal.
9/12/32	5		6.65		1200	Moderately dehydrated.
9/15/32		1.3439	4.93	4.38	948	No dehydration or edema.
3/19/32	6	1.3476	6.74	6.35		Markedly dehydrated—died.
12/ 3/32	7	1.3517	8.00	8.40	1085	Markedly dehydrated.
12/ 5/32		1.3458	5.75	5.36	860	Edema of face, eyelids and arms.
12/15/32		1.3470	5.95	5.98		Normal.
2/ 9/33	8	1.3544	8.80	9.79	932	Moderately dehydrated.
2/13/33		1.3467	5.88	5.82	1344	No dehydration or edema.
2/27/32		1.3513	8.55	8.09		Normal.
2/ 6/33	9	1.3455	5.78	5.20	1396	Moderately dehydrated.
2/ 9/33		1.3448	5.15	4.84	1218	Markedly dehydrated (died).

*Calculated on basis of Neuhausen and Rioch's modification of Reiss' formula. (J. Biol. Chem. 55: 355, 1923.)

and by calculating the percentage from the refractive index, using Neuhausen's modification of Reiss' formula. The refractive index was determined by using the Dipping Refractometer (Zeiss). Four of our nine cases had serum protein readings of 8 gms. per cent or higher, and in all four cases marked clinical dehydration was present. In all cases there was a drop in serum protein concentration with treatment. In at least three of the cases (Cases 2, 3, 4) a sudden drop in serum protein was accompanied by edema, necessitating cessation of treatment, thus emphasizing one of the dangers of this form of treatment. Not all cases with severe dehydration showed a rise in total protein proportionate to the degree of dehydration. It is a known fact that the behavior of serum protein is not always uniform. We feel, however, that daily determinations of serum protein have a distinct value in following the course of dehydration. This is especially true when using the continuous intravenous therapy, when rapid changes in serum protein concentration can be effected and clinical edema thereby produced.

A comparison of serum protein concentrations as determined refractometrically and by the Kjeldahl method, showed a remarkably close agreement (see Table II). This was the experience of Neuhausen and Rioch.[27] Linder, Lundsgaard and Van Slyke,[23] however, found deviations from the results obtained by the Kjeldahl method, as great as 1.5 gm. of total protein in 100 c.c. of serum even in normal cases. In plasma of edematous patients, they found, by refractometry up to double the amount of protein found by the Kjeldahl method. Others[9] obtained similar gross errors. This was apparently due to the presence of excessive amounts of lipoids.

Table II shows the relationship between total protein as determined refractometrically and by the Kjeldahl method; also fluid intake, and a clinical estimate of the degree of dehydration. This table shows several interesting facts: namely, (1) a satisfactory agreement between refractometric and Kjeldahl determinations of serum protein; (2) also that the amount of fluid that the body will tolerate without developing edema, depends upon the initial protein concentration. Hence, the importance of following treatment, at short intervals, with repeated determinations of the refractive index; (3) edema seemed to develop regularly when the serum protein concentration was below 5 per cent.*

Acid Base Equilibrium in Blood Serum.—The existence of acidosis in infants suffering from alimentary intoxication was recognized many

*Owing to lack of material, we were unable to determine albumin globulin ratios.

years ago. Czerny,[3] in 1897, called attention to the presence of "air hunger" in these babies, and the resemblance of their breathing to that observed by Walters in animals poisoned with inorganic acids. Howland and Marriott,[18] however, found no evidence of abnormal acids, nor any appreciable rise in ketone bodies in infants with diarrheal acidosis. Many of their cases had considerable increase in inorganic phophorus. This led them to conclude that in some cases faulty elimination of sodium acid phosphate, due to impaired kidney function, was responsible for the acidosis. Schloss and Stetson[33] also failed to find an appreciable rise in ketone bodies. They concluded that the mechanism of diarrheal acidosis was the same as that responsible for retention of nitrogenous waste, i.e., faulty kidney elimination. Their studies did not include chlorides. The rôle played by chlorides in the acid base mechanism has been emphasized by recent investigators, namely, Schiff, Bayer and Fukuyama,[32] Hartmann,[14] Hamilton, Kajdi and Meeker.[12] Hoag and Marples[15] stressed particularly the relationship between total base and chlorides. Total base and chlorides were determined on all of our cases in each study period. Upon analysis of our data it is obvious that the relationship between total base and chlorides plays a most important rôle in the acid base balance of these babies. Table III shows the rôle played by chlorides, as well as other acid elements in the production of acidosis. Four types of relationship exist, with total base at the pivotal point, as follows:

Group 1. Total base is either normal or elevated, but chlorides are increased to an even higher level. (See Figs. 6 and 9.) Of course, in this group acidosis exists when there is no compensatory decrease of other acid factors to make room for bicarbonate.

Group 2. Total base is reduced, but chlorides are not reduced proportionately, and are at times, distinctly elevated. (See Figs. 2, 3 and 5.) In this group, also, acidosis is generally present.

Group 3. Total base is elevated, with a proportionate rise in chlorides. (See Fig. 7.) In spite of extremely high chlorides, acidosis may be absent.

Group 4. Total base is reduced, with a concomitant drop in chlorides. (See Figs. 4 and 8.) Theoretically, a fifth group might be said to exist, namely, one in which there is a rise in total base with a drop in chlorides leading to alkalosis. Such a condition almost never exists in alimentary intoxication, except possibly when vomiting is an outstanding symptom. Such cases would present a situation analogous to the conditions existing in high intestinal obstruction or pyloric stenosis.[7, 8, 13] Haden and Orr[10] studied the blood of monkeys in

whom the intestine was experimentally obstructed. They found very much the same changes as have been found in man with intestinal obstruction, namely, a fall in chlorides with a coincident rise in CO_2 combining power. They also found an increase in nonprotein nitrogen later. In contrast with this work, Keith[20] showed a constant increase in chlorides in dogs dehydrated experimentally by intravenous injection of hypertonic glucose.

TABLE III

ALIMENTARY INTOXICATION

SHOWING THE RELATIVE IMPORTANCE OF CHLORIDES, SERUM PROTEIN AND UNDETERMINED ACIDS IN THE MAINTENANCE OF ACID BASE EQUILIBRIUM

DATE	CASE NO.	TOTAL BASE MM.	CHLORIDES MM.	BASE BOUND AS CHLORIDES PERCENTAGE	BICARBONATE MM.	PROTEIN MM.	UNDETERMINED ACIDS MM.	
Normal		155	103	66.5	25	18	9	
12/22/31	1	155	107	67	18	21	9	
12/24/31		147	112	76	20	17	0	
1/ 4/32		144	101	70	20	18	5	
1/22/32	2	137	106	77	13	16	2	
1/26/32		148	102	69	26	9	11	
6/ 7/32	3	146	116	79.5	9	21	0	
6/13/32		143	110	76	20	12	1	
7/ 1/32		159	106	66	17	15	21	
7/28/32	4	123	79	65	14	15	15	
8/ 1/32		145	106	72	18	8	13	
8/22/32		149	105	70	21	15	8	
9/12/32	5	146	102	70	20	16	8	
9/14/32		145	106	72	27	12	0	
3/26/32	6	162	132	76	7	16	7	Died
12/ 3/32	7	188	124	66	17	19	28	
12/ 5/32		189	150	79	15	15	10	
12/15/32		149	103	69	25	14	7	
2/ 9/33	8	145	95	65	12	21	17	
2/13/33		152	116	69	19	14	3	
2/27/33		139	104	75	13	21	1	
2/ 6/33	9	154	127	82	11	14	2	chol. 57 died
2/ 9/33		147	115	78	17	13	2	chol. 55 died

We considered only patients with distinctly low bicarbonate values as having acidosis. Table III illustrates the inverse relationship between bicarbonate and chloride values. In only one patient (Case 8) was this relationship absent. In four of our nine cases there was a

definite increase in chloride percentage binding base, following our treatment. This increase was noticed anywhere from two to four days after treatment was begun. The outstanding example of this change is illustrated by Case 7. The initial chloride value was 124 mm. per liter. This rose to 150 mm. after forty-eight hours of treatment. This child was almost moribund on admission, yet there was remarkable improvement clinically in a comparatively short time in spite of the rise in chlorides. Case 4 showed almost as great a rise in chlorides (from 79 mm. to 106 mm.) with similar clinical improvement. Hartmann[14] demonstrated an increase in chlorides of the blood with parenteral use of saline and expressed the fear that this may exaggerate the acidosis through the accumulation of more chloride ions. Our clinical results do not warrant this fear, especially since we were able to establish diuresis early in all cases. Even where chloride concentration does increase, clinical improvement follows rather than the reverse. We may say definitely that the use of saline (with glucose) is not only safe, but essential in replenishing lost electrolytes and in establishing urinary flow. In spite of the striking changes in chlorides in this condition, it is seen that clinical improvement may follow independently of any chloride shift.

Unfortunately, we did not determine P_H. However, the observations of Hoag and Marples[15] show that *marked changes* in P_H occurred almost solely in moribund or fatal cases. Hence, such changes as might have occurred in the majority of our cases could not significantly alter our calculations.

The rôle played by undetermined acids could only be estimated very roughly, as no determinations were made of sulphates, lactic acid and other organic acids. It would seem from our calculations, that they play but a minor rôle in any case. (See case summaries.)

The importance of serum protein concentration in acid base equilibrium also seems to be minor. Only four of our cases showed high enough readings to have any influence. Of these only two had acidosis. The readings for serum protein in these four cases followed generally the values for bicarbonate—a relationship similar to that observed with chlorides. This would tend to minimize the importance of total protein in its influence on acid base equilibrium. (See case reports.)

DISCUSSION OF TREATMENT

It is generally accepted that the administration of fluids is essential in the establishment of normal chemical equilibrium as well as for the restoration of normal water balance. The administration of

fluids by mouth in quantities large enough to accomplish these ends, would only serve to increase the marked gastrointestinal irritability which already exists and would probably aggravate the vomiting. The administration of saline under the skin is often equally ineffectual, as it may not be absorbed rapidly enough due to impaired circulation. The repeated intraperitoneal administration of fluids is not without its dangers and contraindications. The combined use of saline by hypodermoclysis followed immediately by 10 per cent solution of glucose intravenously has proved to be an extremely valuable method at the New York Nursery and Child's Hospital.[15] The use of the continuous intravenous drip, though not a new form of treatment in principle, does offer distinct advantages in fluid administration. We found,

TABLE IV

A COMPARISON OF MORTALITY STATISTICS FROM SEVERAL INSTITUTIONS

AUTHOR OR INSTITUTION	YEAR	NO. OF CASES	MORTALITY %
Monrad[26]	1923	181	21
N. Y. Nursery and Child's Hospital	1925-1928	175	35
Powers[29]			
(a) Comprehensive plan	1926	36	33
(b) No comprehensive plan	1926	19	70
Hartmann[14]	1928	27	88
Mt. Sinai Hospital, New York	10 yr. period preceding 1931	?	64
Hoag and Marples[15]	1931	14	29
Karelitz and Schick[19]	1931	21	14
Present Series	1933	9	22

just as Karelitz[19] did, that the chief advantage of the method lies in the fact that longer periods of gastrointestinal rest are possible; also, once the cannula is in place, much needed physical and mental rest are more easily obtained than by previous methods. The principle and technic are simple enough to make the method within the reach of every hospital. However, constant watching by the person in charge is necessary, due to minor technical problems such as plugging or displacement of the needle, control of the rate of flow or local infiltration. For these reasons we found it necessary to assign a special nurse to each patient.

The evaluation of any method of treatment depends primarily upon our ability to gauge the severity of the disease. Neither clinical data nor chemical determinations on blood seem to be adequate for this purpose in all cases. Patients that on first examination seem to be suffering from only a moderately severe diarrhea—so moderate as to

create a false sense of security—quickly produce disillusionment when the infant develops profound and often fatal intoxication.

On the other hand, patients that have anuria of many hours' duration with marked dehydration, intoxication, moderate depletion of alkali reserve, high nonprotein nitrogen, often respond almost miraculously to therapy.

A priori, one could hardly expect the blood serum to be a very sensitive index of the physiologic disturbance. The blood maintains its chemical composition with remarkable tenacity. Striking changes in composition of plasma with respect to base chloride, bicarbonate and protein do not occur until the water loss is equal to or exceeds twice the total plasma water. The tissue fluids constantly restore the base and chloride lost through vomiting, until this has become so severe that compensation can no longer take place. Only then does plasma begin to reflect loss of water and minerals from the tissues. This explains the failure of plasma to reflect the severity of the clinical condition except when patients are in extremis.

Lack of material prevented us from making a comparative study of the value of the different channels of fluid administration. However, good results were obtained with the continuous intravenous drip using 5 per cent glucose and normal saline. The technical difficulties have been discussed by Karelitz and Schick.[19] In patients who recovered there appeared to be a prompt improvement in the clinical condition, and restoration of chemical equilibrium in blood proceeded more slowly.

More specifically we may say that (1) diuresis was established early in all cases; (2) dehydration was combated and lost body electrolytes were restored; (3) diarrhea was controlled in almost all cases; (4) acidosis, when present, was controlled both clinically and chemically without the use of sodium bicarbonate injections as was recommended by early and more recent investigations.[33, 18, 14]

In conclusion, we wish to emphasize that in offering our results, we do it fully realizing the necessity of taking into consideration such factors as seasonal variation, severity of cases, variations in locality, average age of the group, the presence of marked infection which may influence the mortality of any given series of cases.

CONCLUSIONS

1. Administration of glucose and saline solution by continuous intravenous drip is a reasonably safe procedure.

2. Dehydration is rapidly corrected and diuresis reestablished.

3. Adjustment of inorganic equilibrium of blood may require several days. Clinical improvement usually precedes chemical readjustment.

4. Diarrheal acidosis in our cases was due either to relative or absolute increase in chloride or to decrease in fixed base in agreement with previous observation.

5. Increase of nonprotein nitrogen disappeared promptly with reestablishment of diuresis.

6. No final conclusions can be drawn as to therapeutic value of this method of administration because of lack of sufficient number of cases.

7. The amount of fluid required to overcome dehydration would seem to be less than when other channels of administration are used. There is real danger of producing edema because of rapid blood dilution.

We wish to acknowledge our indebtedness to Dr. S. Moskowitz, Miss D. Luntz, Miss M. Edelman, and the Resident House Staff for their valuable assistance.

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Original Communications

DILATATION AND HYPERTROPHY OF THE HEART IN INFANCY DUE TO PARENCHYMATOUS MYOCARDITIS

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MARKED dilatation and hypertrophy of the heart in infancy presents many difficulties in diagnosis. As to the true nature of this condition, confusion still exists. That enlargement of the heart may develop secondarily to definite causes is not questioned. In the past, however, the term idiopathic was applied to a majority of cases. For this group, a satisfactory anatomic and causative explanation could seemingly not be found. A critical review[1] of published reports of so-called idiopathic enlargement of the heart in infancy has disclosed in many instances no mention of histologic studies, or else the presence of factors possessing primary etiologic significance, such as congenital vascular anomalies, acquired valvular and pericardial lesions, infections, and anemia. Customarily classified, also, as idiopathic, has been a type of cardiac dilatation and hypertrophy, which present-day work stresses, is actually due to an intrinsic myocardial lesion, apparently toxic in origin. Careful examination has revealed in recently studied cases varying degrees of parenchymatous degeneration of the heart muscle, interstitial round cell infiltration, and fibrosis. A clear-cut history of antecedent infection or toxemia has often been lacking.

The object of this paper is to report two cases of pronounced dilatation and hypertrophy of the heart showing different stages of parenchymatous myocarditis, which were observed in nurslings during the past year. Because of the unequivocal character of their histologic changes and their definite relationship to known infections, these cases may be of some help in clarifying the general problem of cardiac enlargement in infancy.

CASE 1.—*History*—S. A. A.; a white girl, American, aged one year, was admitted to the Buffalo Children's Hospital in the service of William J. Orr, October 28, 1932, because of dyspnea and "weakness" of seven days' duration. The family history was essentially negative. The patient was the fourth child. She was born at term and weighed 7½ pounds. The mother suffered from no illnesses

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during pregnancy; delivery was normal. No convulsions or cyanosis occurred at or after birth. The child was breast fed; cod liver oil and orange juice were given after the fourth month; the first tooth appeared at six months. She walked at twelve months. Six weeks before hospital admission, the patient became ill with fever and cough. These complaints persisted for three weeks. Examination of the chest showed scattered râles; the heart was not found to be enlarged. A diagnosis of bronchopneumonia was made. For two weeks following the termination of this respiratory infection, the child was "perfectly" well. During the next week the respirations became labored; cough and anorexia appeared. No fever was observed.

Physical Examination.—Temperature 100 per rectum, pulse 140, respirations 60. Well-developed, poorly nourished white female infant lying in bed, dyspneic and coughing, acutely ill. Cyanosis was marked. The nose was filled with a mucopurulent exudate. The pharynx was injected; postnasal discharge was seen. The cervical glands were palpable. The left lower chest showed decreased expansion, dullness anteriorly and posteriorly, and absent breath sounds. The heart was markedly enlarged, and very rapid. A systolic murmur was present. The liver was palpable. Laboratory studies included: throat smears which were negative for diphtheria bacilli; hemoglobin (Tallquist) 72 per cent; white blood count 19,750; polymorphonuclear leucocytes 64 per cent; lymphocytes 34 per cent; basophils 2 per cent; x-ray examination showed enlarged heart. A diagnosis of pericarditis with effusion was considered. The child died three days following hospital admission.

Autopsy.—One-half hour after death. The anatomic diagnosis was: marked dilatation of the heart and slight hypertrophy, especially of the left ventricle; slight endocardial fibrosis of the left atrium and ventricle; compression atelectasis of both lungs; lobular pneumonia (gram-positive diplococci) in left upper lobe; bulging deformity of the left chest; low position of left lobe of liver, with indentation on its superior surface; passive congestion of liver, spleen, and kidneys. The thymus weighed seven grams. The line of ossification was normal.

When the chest was opened, the pericardium was found to be distinctly distended. No adhesions were present. The pericardial fluid was straw-colored and slightly increased in amount. The surfaces of the pericardium were smooth and glistening. The heart was markedly enlarged, spherical in shape; weighing 85 grams. The transverse diameter measured 7 cm.; vertical 9½ cm., and the anteroposterior diameter 6 cm. The right atrium was dilated. The right ventricle measured 8 cm. in circumference; its wall at the base 0.2 cm. The musculature was flabby. The left atrium was dilated; the left ventricle measured 9.5 cm. in circumference; the wall at the base measured 0.8 cm. All valves were smooth and delicate. The coronary vessels were normal. The foramen ovale and ductus arteriosus were closed. The aorta measured 2.6 cm. above the aortic valves; at the isthmus 1.4 cm. As the valves appeared entirely normal, the extensive dilatation of the heart was considered to be due to a myocardial damage, in the sense of an apparently diffuse myocarditis, as occurs in adults, and in children following infectious disease.

The heart was fixed in Craig solution. Blocks of tissue were cut from various parts of both ventricles and atria. Hematoxylin-eosin, Giemsa, van Gieson, and sudan III stains were made on frozen sections. Methylene blue and gram stains were used on paraffine sections.

Microscopic Examination.—In sections examined, the pathologic changes were found to be rather uniform in character. They were most pronounced in the wall

of the left ventricle. The inner and outer zones of the myocardium showed poor staining quality. The endocardium was slightly thickened. The inner muscle zone demonstrated a diffuse vacuolar degeneration, the vacuoles varying in size and extension. In some fibers they were restricted about the nucleus, while in others they extended for a great length along the fibers. The nuclei in vacuolated fibers were generally oval and pale, bordering eccentrically on the membrane of the muscle fibers, or occupying a central position in the vacuoles. Their chromatin material was sometimes scattered in coarse round granules or arranged in a central longitudinal position. The sheaths of the vacuolated fibers were well preserved. Within

Fig. 1. Fig. 2.

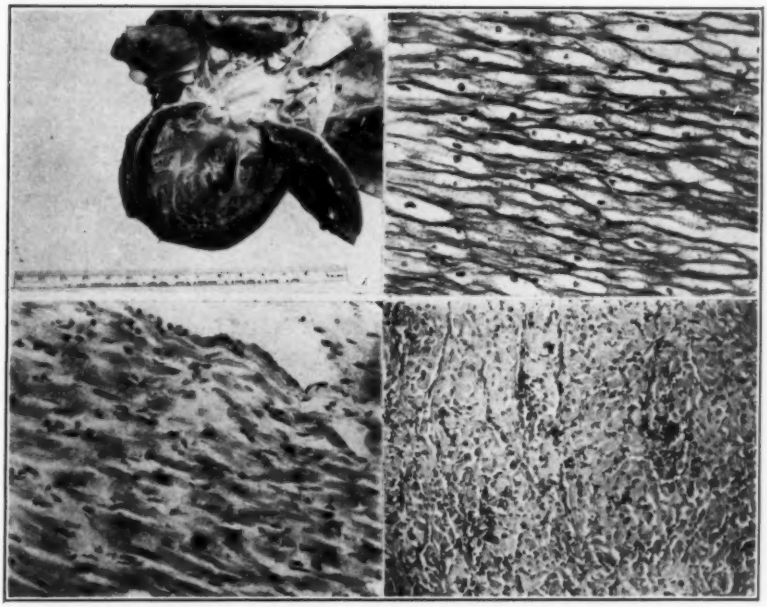

Fig. 3. Fig. 4.

Fig. 1.—Case 1. Internal view of left ventricle.
Fig. 2.—Case 1. Vacuolar degeneration in inner muscle zone. H.P.
Fig. 3.—Case 1. Patchy degeneration in middle zone. Note also large hyperchromatic nuclei. H.P.
Fig. 4.—Case 1. Interstitial round cell collections in outer zone. L.P.

the sheaths forming the boundaries of the vacuoles, were frayed fibrillar structures showing no striations, and cellular débris. The fibers themselves appeared swollen; the vessels here were injected. The middle zone of the myocardium showed better staining qualities. In the muscle fibers of this zone many large nuclei of bizarre shape, generally rectangular and deeply staining were seen. Indented nuclei were present; fibers with two nuclei were also observed; scattered fibers showed longitudinal splitting. Slight interstitial edema was present. Here and there throughout the middle zone were small patches of muscle fibers, poorly stained and granular in appearance with loss of striations. The outer muscle zone also showed vacuoliza-

tion; many of the fibers appeared to possess a boiled, coagulated appearance. The nuclei were massive and pale. Distinct interstitial edema was present. Slight focal round cell infiltration was noted especially beneath the epicardium and around the vessels. Cross-sections of muscle fibers showed many small fat granules. There was distinct edema of the subepicardial tissue. No bacteria were demonstrated by stains; fibrous tissue by van Gieson stain was not appreciably increased.

Sections from spleen and kidneys showed distinct passive congestion. The liver showed areas of regressive changes, with slight leucocytic reaction in the capillaries. Numerous small fat granules were scattered throughout the liver cells.

CASE 2.—*History.*—T. W., a white boy, American, aged six months, was admitted to the Buffalo Children's Hospital in the service of Douglas P. Arnold, March 18, 1932, because of dyspnea and cyanosis of five weeks' duration. The family history was essentially negative. The patient was a first child, born at 7 months' gestation, weighing 3 pounds, 14 ounces at birth. During pregnancy the mother suffered no illnesses. Delivery was not instrumental. No convulsions or cyanosis were observed at or after birth. Though nursing was difficult at first, the child developed uneventfully to the age of three months. At this time he became acutely ill with stomatitis, vomiting, and fever. Examination of the chest revealed no abnormalities; no cyanosis was present; illness lasted three days. Eight weeks later the boy became suddenly dyspneic and cyanotic. After a short time the acuity and severity of the symptoms abated somewhat but breathing remained rapid and shallow; vomiting occurred on several occasions. Examination of the chest at this time showed a large "heart"; a diagnosis of pericarditis with effusion was made. Following paracentesis, in which only bloody fluid was obtained, the child became intensely cyanotic and dyspneic. At this time he was admitted to the hospital.

Physical Examination.—Well-developed, well-nourished, white male infant, markedly cyanotic and dyspneic, acutely ill. Superficial lymph nodes were not palpable. The chest was well formed; no beading was present. Fingers showed no clubbing. The left chest showed dullness anteriorly and posteriorly. The breath sounds were exaggerated; no râles were heard. The heart was markedly enlarged; rate rapid; sounds of fair quality; no murmurs were heard. Liver and spleen were not palpable. The child died three hours after admission to the hospital.

Autopsy.—One and one-half hours after death. The anatomic diagnosis was: marked dilatation and moderate hypertrophy of the heart, especially of the left ventricle; endocardial fibrosis of the left atrium and ventricle; compression atelectasis of both lungs, especially of the left lower lobe; recent petechial hemorrhages in pericardium and capsule of thymus; hemopericardium (70 c.c.); slight anemia; slight hyperemia of the pharynx. Small Meckel's diverticulum. The thymus weighed 8 grams. The line of ossification was pearly gray and regular.

When the sternum was removed, the pericardium was found to be distinctly distended; no adhesions were present. The pericardial sac contained about 70 c.c. of bloody fluid. There were a few hemorrhages in the epicardium. The heart was markedly enlarged and globular in shape, weighing 65 grams. The transverse diameter measured 5.5 cm. The vertical 9 cm. The circumference at the base measured 12 cm. The right atrium appeared normal; the right ventricle was moderately dilated; the circumference measured 4.6 cm., its wall at the base 0.2 cm. The left atrium was slightly dilated. The endocardium showed slight fibrosis. The left ventricle was distinctly dilated and hypertrophied. Its circumference measured 7 cm.; the wall at the base 0.8 cm.; the endocardium was grayish white and opaque.

The valves were intact and translucent. The foramen ovale and ductus arteriosus were closed. The coronary vessels were normal. The aorta measured 2 cm. above the valves; 1.2 cm. at the isthmus. Again in the absence of signs of endocarditis on the valves, a diffuse chronic myocardial lesion was expected.

Microscopic Examination.—As in the first case, the most pronounced pathologic changes were found in the wall of the left ventricle and in the inner and outer zones of the myocardium. The endocardium showed a distinct fibrosis. The muscle fibers in the inner zone were wavy and pale stained. They were separated from each other by a fibrillar connective tissue and a slight interstitial edema. Scattered poorly stained patches revealed various phases of regressive changes. Mus-

Fig. 5.

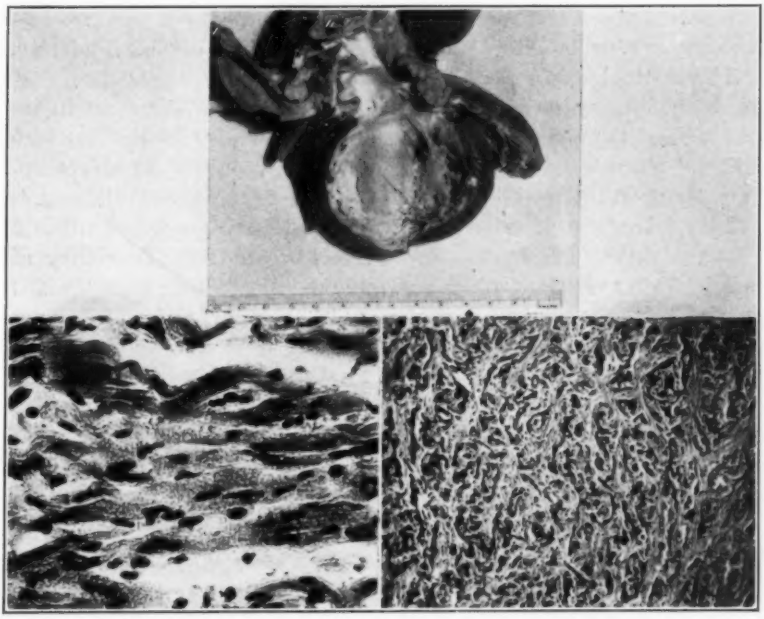

Fig. 6. Fig. 7.

Fig. 5.—Case 2. Internal view of left ventricle.
Fig. 6.—Case 2. Granular degeneration in inner zone. H.P.
Fig. 7.—Case 2. Interstitial fibrosis in outer zone. L.P.

cle fibers appeared swollen and in places showed a loss of cross striations. Sometimes the muscle fibers for a short distance were pale and yellow in color, their cytoplasm granular and lumpy. Occasionally, granules staining deeply with eosin were present. In places, the cytoplasm had entirely disappeared; the sarcolemma alone remaining. In degenerative areas the nuclei were large, oval and pale. The chromatin material was arranged in granules showing no constant geometric pattern. Occasionally both the cytoplasm and sarcolemma were entirely disintegrated. In the remaining gap could be seen cellular and nuclear débris. Many nuclei

showed fragmentation and eccentric positions. In preserved portions of myocardium, the nuclei were large, rectangular and trapezoidal in shape, sometimes peripheral in position, and deeply stained. Double nuclei were visible. In the outer zone, there was a marked increase of interstitial fibrous tissue with many spindle and round cells. The vessels appeared dilated. The muscle fibers themselves in this region were small in diameter and distorted in shape. Sections parallel to the surface did not show extraordinary changes. Sections from the right ventricle showed areas of acute degenerative changes with focal cellular infiltration, especially of leucocytes. No bacteria were seen.

Sections from liver, spleen, and kidneys revealed slight passive congestion. One adrenal showed a small cortical adenoma.

COMMENT

With the absence of any gross anatomic abnormality, vascular, pulmonary, or renal in nature, the two cases of marked cardiac dilatation, and hypertrophy here reported might have been designated at first scrutiny as examples of "idiopathic" enlargement of the heart in infancy. But thorough histologic examination revealed in each instance different stages of diffuse parenchymatous myocarditis dependent apparently upon the severity and extent of the initial myocardial insult, and the subsequent duration of life. The first case represented an early phase of rather diffuse parenchymatous myocarditis with swelling of muscle fibers, vacuolar, fatty, and granular degeneration, and round cell infiltration. Interstitial fibrosis and hypertrophy of muscle fibers were at the most only slight. In the second case, later degrees of myocardial damage were manifested by distinct fibrosis, but still some patchy areas of degeneration and necrosis were present. Moderate hypertrophy of muscle fibers and endocardial fibrosis had already taken place. In both cases the most pronounced regressive lesions were found in the left ventricle, and in the inner and outer zones of the myocardium —the inner zone containing evidences of more active changes.

In view of the fact that no bacteria were seen in examined tissues, the most likely explanation for the degenerative myocardial changes would be the action of a toxin, bacterial or nonbacterial. The chronologic relationship of the fatal cardiac complaints in each case to an antecedent infection must be considered as more than a mere coincidence. For, until a short interval following the subsidence of the bronchopneumonia and stomatitis, both of which were observed and diagnosed by physicians, neither child had ever suffered cardiorespiratory difficulties; nor had enlargement of the heart been detected by physical examination at various times. Added substantiation of the primary etiologic rôles played by the antecedent acute infections is given by the age and activity of the histopathologic findings. In the first case, where death occurred six weeks following bronchopneumonia, the myocardial alterations were recent and still active; hypertrophy was not outstanding.

On the other hand, the microscopic changes in the second child, who died twelve weeks following stomatitis, illustrated already signs of reparation in the presence of distinct fibrosis and moderate hypertrophy.

Comparative analysis, moreover, emphasizes the essential similarity between the myocardial degeneration observed in our cases and that seen in other infections, especially those noted for production of a severe toxin, e.g., typhoid fever, influenza, diphtheria, scarlet fever,[2] stomatitis epidemica in cattle vesiculosa.[14] Studies of diphtheritic hearts,[4, 5, 6] in particular, have pointed out the occurrence of extensive vacuolar and hyalin degeneration and round cell infiltration, most prominently in the left ventricle and inner muscle zone. No conclusive evidence exists that diphtheria was involved in either of our cases. The stomatitis in the second case did not present the bioptic characteristics of this disease, and, in the first instance, nose and throat smears were negative for diphtheria bacilli. Diffuse severe myocardial degeneration has also been noted in animals afflicted with azoturia,[6] an infectious toxemia, and in experimental conditions following the injection of lactic acid[7] and bacterial toxins.[8] Among the cases of marked enlargement of the heart due to parenchymatous myocarditis reported in infants and young children, some were observed after eczema,[8] and poliomyelitis[10] respectively. In a number, however, no definite history of an antecedent infection or toxemia could be obtained. Stoloff[1] suggested that in infancy many toxic conditions exist which are occult, but nevertheless exert a deleterious effect upon the heart. In cases of parenchymatous degeneration in the newborn, the probability of an intrauterine infection or toxemia must not be overlooked.

By a correlation of the clinical and pathologic data in our two cases, the pathogenesis of parenchymatous myocarditis with marked enlargement of the heart can be summarized as follows: (1) Relatively acute parenchymatous degeneration and necrosis of the heart muscle consequent to the action of a bacterial (or other) toxin; (2) reactive interstitial inflammation appearing some time after the first myocardial damage, ostensibly in phagocytic and autolytic response to irritant muscle débris; (3) later, gradual reparative fibrosis following removal of detritus, and dependent upon the extent of the original degeneration; (4) attempts at muscle regeneration, hypertrophy of the less damaged fibers, and endocardial fibrosis. The mechanism of dilatation and hypertrophy is self-evident. In a single heart then, degeneration, inflammation and reparation or scar formation may be present to a more or less similar degree. In different hearts, all properly classed as examples of parenchymatous myocarditis, one of these processes may be so prominent as to appear individually to be of primary importance. Such

diverse pathologic pictures, merely manifestations of one disease at various stages, have probably tended to hinder somewhat the development of a unified conception of cardiac enlargement due to parenchymatous myocarditis.

An increasing knowledge of the etiologic factors and gross and finer pathologic changes of marked enlargement of the heart in infancy, gained in recent years, leads to the conclusion that under the term "idiopathic" cases have been included which may have been dependent upon several different causes. Further, it seems probable both from theoretical considerations and from a survey of published reports that many instances of enlargement of the heart, called "idiopathic," really fall into a category due to parenchymatous myocarditis. In 1928 Stoloff reviewed 28 cases of idiopathic enlargement accompanied by histologic reports and compiled 6 which revealed myocardial disease. In three cases[11, 12, 13] reported since, evidences of parenchymatous degeneration were present. Marked enlargement of the heart in infancy might more profitably be classified from an etiologic and anatomic point of view. Continued use of the term "idiopathic" can only offer the clinician an unsound basis upon which to predicate his diagnosis, treatment, and prognosis.

The observation within one year of two cases of marked cardiac dilatation and hypertrophy due to parenchymatous myocarditis indicates that this condition possibly occurs more frequently than is commonly believed. To account for an enlarged heart appearing shortly after acute infection or toxemia, parenchymatous myocarditis ought to be considered. Noteworthy clinical features in our two cases included history of antecedent infection, sudden onset of dyspnea, cyanosis, anorexia and vomiting, bulging deformity of the left chest, large heart, apical systolic murmur, low position of the liver, and pulmonary atelectasis. In each case pericarditis with effusion was first suspected. Deaths were due to hemopericardium, following paracentesis and bronchopneumonia.

SUMMARY

Two cases of marked dilatation and hypertrophy of the heart observed in infants, aged 1 year, and 6 months, respectively, are reported. Histologic examination revealed in each instance different stages of diffuse parenchymatous myocarditis. Cardiac symptoms and enlargement of the heart first appeared following acute infections (bronchopneumonia, acute stomatitis).

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THE PRESENT STATUS OF SERUM TREATMENT IN ACUTE POLIOMYELITIS

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THE use of immune serum in the treatment of acute poliomyelitis has assumed such a degree of prominence that it seems well to render an accounting of its achievements. Such an accounting must of necessity take into consideration the fundamental premises of the theories involved and the difficulties encountered both in the application of these theories in actual practice and in the compilation of the results.

Immune serum therapy in this disease is based upon a large array of experimental data which prove conclusively that the virus can be neutralized *in vitro* by the addition of serum obtained from individuals who have recovered. These experiments are confined to monkeys, because these animals alone are susceptible to the disease, at least in the form in which it appears in man. Furthermore, it has been shown that if such immune serum is injected into a monkey within twenty-four hours of an injection of the virus, the animal may be protected from the disease, either completely or to such an extent that it runs a milder course than would be expected from the dose of the infective material. We need not go into these laboratory findings, for they are numerous and well known. It is, however, necessary to bear in mind that the experimental disease is induced in monkeys by injection of the virus directly into the cerebrum, by intravenous injections, or by prolonged applications of virus-soaked pledgets within the nares, along with an artificial disturbance of the function of the choroid plexus by injecting a foreign substance intraspinally. Thus, the experimental disease is brought about by measures more drastic than the natural means of infection in man. More recently Flexner has been able to inoculate monkeys by simple nasal instillation of a potent virus.[1] However monkeys do not contract the disease from each other by ordinary contact in cages.[2]

From the facts noted above we might infer that the monkey presents greater natural barriers to the disease than man. But recent work, notably by Aycock and Kramer,[3] has shown that a high degree of immunity to this disease exists in adult human beings. In fact, this degree of immunity is comparable with that found in adults against measles. It has, therefore, been assumed that this immunity is acquired by the survival of infection as in measles. Furthermore, when poliomyelitis invades a community in which it has not previously appeared, as on the

From the Haynes and Evans Memorials, the Massachusetts Memorial Hospitals, Boston, and the Department of Pediatrics, Harvard Medical School.

island of Nauru,[4] we have evidence of a high vulnerability of the adult population, precisely as in the case of measles when it invaded the Faroe Islands. This comparison with measles is also substantiated by the greater incidence of poliomyelitis among adults in the country as compared with the city, while we all remember the high incidence of measles among the army recruits from the country districts. It is roughly estimated that nine-tenths of the population in all large cities has had measles before the age of sixteen.

This comparison between the acquired immunity of poliomyelitis and that of measles involves the hypothesis that poliomyelitis is a complication of a very widespread general infection, and that it is only when the central nervous system becomes invaded in the course of this infection that poliomyelitis as such occurs,* and that the infection is of such a character as to permit of a widespread immunity through a majority of very mild abortive cases or through many healthy carriers.[5] Such an hypothesis enables one to explain its distribution in the course of epidemics, as well as the greater immunity among adults, especially in urban populations. Indeed, such a conception greatly influences our procedures in combating the disease, because this knowledge of increased immunity through age affects our quarantine of contacts. Furthermore, it provides us with the logic for a source of supply of immune serum, particularly in the form of fresh whole blood from a parent when convalescent serum is not available—a practice frequently employed in the prevention of measles. There is, of course, the risk that the normal adult serum used may be poor in immune bodies.† But we must not lose sight of the fact that our pooled convalescent poliomyelitis serum is not a standardized product like diphtheria antitoxin, and that the dosage used is a purely empirical formula.

Thus, we are justified in employing convalescent polioserum and normal adult blood serum on the ground of the probable existence of immune bodies in the supply used, because such supplies in general have proved efficacious in neutralizing the virus in tests on monkeys. Such a premise, however, does not offer any guarantee that a given immune serum—even of proved efficacy in the laboratory—can exert a curative action in man after the incubation period has been passed and the nervous system has been invaded. We are not in a position to arrive at any positive conclusions as to whether this immune poliomyelitis

*Faber dissents from this view and defends the theory that poliomyelitis is an essential nerve system disease throughout its course. Faber, H. K.: Poliomyelitis as an essential nerve system disease throughout its course. Science 75: 198, 1932.
It has been suggested that the increased immunity to poliomyelitis in adults might be attributed to a general raising of the powers of resistance through the survival of the common diseases of childhood which confer lasting immunity.

†It appears that individuals who have been in close contact with poliomyelitis without contracting it are apt to possess an even higher power of neutralizing the virus *in vitro* than do those who have recovered from an attack, as is the case in diphtheria. Shaughnessy, H. J., Harmon, P. H., and Gordon, F. B.: J. Prev. Med., p. 463, 1930.

serum can act like scarlet fever convalescent serum, which is preventive as well as curative, or whether it acts like measles convalescent serum, which is a preventive if used in the incubation period, but exerts no beneficial influence after the symptoms of measles have appeared. Park[6] has reminded us that no convalescent immune serum has as yet been shown to be effectual in any but a preventive manner when a filterable virus is the etiologic factor. This explains the difference in the results above mentioned regarding scarlet fever serum and measles serum.

This brings us to the manner of administration of the serum, and again our theories as to procedure revert to experiments in protecting monkeys. In experimental work, a combination of intravenous and intraspinal injections has given more satisfactory results than other methods; hence the tendency to adhere to this combined method in practice. Furthermore, the use of intraspinal injection of immune serum in cerebrospinal meningitis has led to the assumption that this method should be efficacious in poliomyelitis. This reasoning is in part fallacious because the pathology of the two diseases is not similar. In cerebrospinal meningitis we have a purulent infection of the meninges, and the injected serum comes in direct contact with the inflamed and infected areas, while in poliomyelitis the lesions lie within the medulla and cord.

It is of importance to review the nature of the poliomyelitis lesion in order that we may understand as well as possible the task of trying to assist the patient. The infection is thought to start usually in the upper respiratory tract, although it may also invade the gastrointestinal tract. The first evidence of involvement of the central nervous system consists in meningeal irritation, giving headache, rigidity of the neck and spine, and muscular tremors. This constitutes the preparalytic stage, in which the disease is not infrequently arrested. The pathologic process here consists of an inflammation of the meningeal vessels associated with proliferation of their lining cells, and often an increased amount of spinal fluid which may contain added cellular elements. Then comes the paralytic stage, the result of the injury to motor nerve cells. Here again, the primary pathologic factor consists in a proliferation of the cells lining and coating the meningeal vessels. These vessels supply the interior of the medulla and cord, and some, notably those supplying the anterior horns, appear to be more susceptible to these changes than others.

At this point we enter into speculations regarding the cause of injury to the nerve cells. Such speculations, however, must evolve from the recognizable pathologic pictures with which we are familiar. At the site of a fresh lesion we can see the vessels exhibiting proliferation of their lining cells to the point of occlusion. Minute hemorrhages may be present. The nerve cells supplied by these vessels are necrosed or

undergoing necrosis. From this picture of a cross-section of the cord we may infer that we are witnessing in the early paralytic stage of the disease the manifestation of this pathologic picture. Shall we imagine the nerve cell injured or destroyed as the direct result of contact with the virus? Or shall we take into account the prime pathologic factor; namely, the blocking of the vessels that supply this nerve cell through endothelial cell proliferation? The latter explanation would give us a partial or complete starvation and account for the temporary and permanent injuries which may follow. Furthermore, if we prefer to adhere to the direct action of the virus, we may well imagine that a blocking of the venous supply of this area would dam up the virus about the nerve cell and augment such direct injury from the virus. Thus, we must consider injury to the motor nerve cell by starvation, by venous obstruction, by direct action of the virus, and by hemorrhage. The result of all this is muscular paralysis and an increased amount of spinal fluid, which on lumbar puncture may come away under pressure, and the increased cellular content may give this fluid the characteristic ground-glass appearance.

With such a conception of the disease in mind, what are we to expect from the injection of immune serum by any route? Our expectations must conform to the pathology and the clinical results obtained. The spinal fluid deserves particular attention. The choroid plexus is considered to be the hydraulic stabilizer of this fluid.[7] This choroid plexus also normally prevents bacteria and viruses (as well as antibodies) from reaching the spinal fluid. In poliomyelitis the choroid plexus fails to function normally. Once the infection gains access to the meningeal vessels, the increased volume of cerebrospinal fluid would appear to originate from the inflammatory areas about the meningeal vessels. In the affected areas in the gray matter of the anterior horns it must be conceded that the flow of fluid is toward the periphery of the cord, unless we are to imagine that the normal outward flow[8] of spinal fluid from the pericellular spaces through the perivascular spaces into the subarachnoid space is reversed, and there appears to be no valid reason for assuming any such reversal.

The basis of intraspinal serum therapy must be some such conception of inward flow unless we are to assume that the capillaries pick up immune bodies in the subarachnoid space and carry them inward toward the ganglion cells, or that these immune bodies gain access to the general blood supply through the choroid plexus.[9] But here again there is no evidence that the permeability of these capillaries would permit a distribution of these immune bodies in the anterior horns.

In short, we have no grounds for supposing that immune bodies injected at the site of a lumbar puncture could find their way against the fluid flow toward the anterior horns, nor are there any reliable

grounds for assuming that the immune bodies would be absorbed by the choroid plexus or other meningeal vessels. The most that could be expected is that the immune bodies would be diffused throughout the surface of the cord and there neutralize the toxicity of the free virus. But our conception of the pathology of the situation does not make this of much assistance within the cord. It is not enough to refer to the efficacy of intraspinal serum therapy in protecting monkeys, because here the situation is far less complicated than that presented by the manifestations of the natural disease in man. Nevertheless, this seems to be the only premise upon which this method of administering immune serum is based. Thus its use is largely an empirical practice for which no entirely satisfactory theory has been advanced.

It has been argued that the intraspinal method may disturb the choroid plexus. Macnamara[10] has warned against draining off the fluid without replacing an almost equal amount of immune serum for fear of disturbing this choroid plexus. But this immune serum is not a normal constituent of the spinal canal. It is distinctly a foreign substance and especially so when preservatives are added. Thus it produces a meningeal irritation, as evidenced by the increased cell count following the injection. Furthermore, the choroid plexus is already disturbed by the virus in the preparalytic stage. Just what effect any further disturbance through spinal drainage or the presence of serum can produce, if any, is purely a matter of speculation, but, nevertheless, a question worthy of consideration and investigation. Furthermore, the advisability of irritation of the meninges in any stage of the disease is open to question quite as much as the danger of spinal drainage. These theoretical dangers are not generally substantiated by clinical experience.

The intravenous method of administering immune serum would seem to be the more plausible. If we are correct in assuming that we are dealing with a generalized infection, this method would seem to be the more direct attack. If, on the other hand, we prefer to look upon the disease as localized in the central nervous system, then again we must concede that the most direct approach to the lesions, whether in the meningeal vessels or in or about the motor nerve cells, would be achieved through the blood stream. But here the term "approach" must be qualified, because, although the immune bodies are brought into the affected blood vessels, they cannot pass through the occluded portions which are responsible at least in part for the injury to the nerve cells. Nor is there any valid reason for supposing that these immune bodies could migrate through the lumen of a meningeal vessel to bring help to a nerve cell threatened with toxic necrosis. Consequently, here again our method is based upon the experiment of protecting a monkey, but

prevention, as we have already seen, is not always synonymous with the cure or alleviation of an established disease following an incubation period.

Thus, on hypothetical grounds, both the intraspinal and the intravenous route would seem to offer some hope of beneficially modifying the disease in the preparalytic stage, but we cannot imagine that it is possible to bring any direct help to the injured nerve cells in the paralytic stage; although if such help is possible in this early stage, then, indeed, we ought to be able to prevent the extension of paralysis, especially in the deadly ascending types. This, however, is not the case in practice, even when the combination of these two routes is used.[11] The intramuscular and subcutaneous routes need only be mentioned as offering a slower approach in a condition where a prompt neutralizing action would seem to be desirable.

Rosenow's serum presents other matters for consideration. Rosenow and his associates[12] claimed to have isolated a pleomorphic streptococcus from spinal cords of autopsied poliomyelitis cases, and with this organism to have produced not only poliomyelitis in rabbits, but also an immune horse serum which they claimed effectually prevented experimental poliomyelitis in monkeys and rabbits. In the first place, their experimental work has not been corroborated by other investigators, and in the second place, their use of other animals than monkeys has brought forth much criticism of their observations. The clinical reports[13] obtained with this serum, however, appeared to overweigh these objections. But while these reports in themselves may appear to favor Rosenow's serum, we shall see that when these figures are placed side by side with the figures obtained from other methods, the efficacy of this serum is not apparent.

Others, notably Kendall, have claimed to grow the virus of poliomyelitis on special media, and caused it to shift into a visible bacterial form.[14] But all this work has also failed of confirmation by others. The question, of course, is whether a virus can be metamorphosed into a bacterial form. Bacteria may change into filterable forms, but they remain bacteria, and in this case the experiments start with bacteria of questionable etiologic relationship.

In discussing Rosenow's serum I have on several occasions called attention to the treatment accorded to Paul Moser[15] of Vienna, who in 1902 obtained a streptococcus from the heart blood of a fatal case of scarlet fever, and with this strain produced an immune horse serum which he used with striking success in eighty-one cases of scarlet fever. His results parallel those obtained with our modern scarlet fever antitoxins, and both Dochez and the Dicks some twenty years later gave full credit to Moser as the pioneer. But Moser's serum was criticized and

neglected because he had failed to establish this strain of streptococcus as the etiologic factor. The tone and phrases of Jochmann[16] and others toward Moser are remarkably similar to those used by Draper[17] toward Rosenow.

In a limited sense Rosenow is in a somewhat similar situation now to that of Moser before the corroborative work of Dochez and the Dicks. There are, however, significant differences. In the first place Moser's streptococcus serum was decidedly effective in early scarlet fever as shown by control charts, while any such constant improvement with Rosenow's serum in early poliomyelitis is not so apparent. Another difference lies in the complexity of Rosenow's claim, in that he assumes not only to have isolated a bacterial cause of poliomyelitis, but that this causative agent exists in a bacterial as well as in a filtrable form, neither of which assertions has been satisfactorily confirmed by experiment though the attempts have been innumerable. Thus, while Moser's work was not adequately checked for some twenty years, Rosenow's work has been subjected to an array of investigations over the past thirty years with results which challenge not only the efficacy of his serum but the validity of his hypothesis. However, inasmuch as there are still some things to be learned about the etiology of scarlet fever, and much more to be learned about the etiology of poliomyelitis, it is barely possible that the comparison of these two investigators might some day become more pertinent than it is now. Suffice it to say that whether or not the Rosenow serum appeals to us, the fact that it is a marketable product is a potent factor in its use, in view of the demand for serum therapy.

In attempting to evaluate any therapeutic measure in an infectious disease, two distinct methods are employed. The more modern method is to run two parallel series under as nearly equal conditions as possible, one series to consist of those cases treated by the method under consideration, while the other series serves as the control. If an adequate number of cases is used, and the conditions imposed are fairly carried out, one has a right to expect trustworthy information which can then be formulated in the conclusions from the comparative results obtained. It so happens, however, that the unknown factors in such an experiment may yield misleading results. One of these unknown factors is the summation of the natural resisting forces of the individual. Under this head we may have to consider the portal of entry and its condition at the time of infection, as well as conditions elsewhere in the body which may be favorable or unfavorable to the spread of the infection. Another unknown factor comprises the dose of the infective agent together with its virulence. The variations in these unknown factors give rise not only to a wide variation in the severity of the same infection in different

individuals, but also to wide variations in the severity of epidemics. Furthermore, because of these unknown factors it is impossible to run a control series where the internal factors can be guaranteed to be equal to those in the treated series, although the external factors may be in all respects equal or very nearly so. Consequently, it is the presence of these unknown variables within the patients which it is necessary to keep in mind in any attempt to evaluate clinical results.

The other method of determining the value of a therapeutic measure is to collect all the available statistical results obtained under a given treatment and to compare these with the statistical results obtained from other methods. Under these circumstances one encounters a perfect infinity of variable extrinsic factors which bear favorably or unfavorably on the results. Chief among these extrinsic factors is the time element concerned with the stage of the disease in which the patient comes under observation and treatment. Another factor of importance is the diagnostic knowledge and skill of the observer, together with his facilities and skill in handling those complications resulting from the disease which are quite apart from the method one is attempting to evaluate.

Both of these methods have been employed in attempting to determine the value of serum treatment in acute poliomyelitis. The modern method with control series was carried out by Kramer, Aycock, Solomon, and Thenebe[18] and by Park.[19] The results obtained from their clinical experiments offer no first-rate proof of the value of convalescent serum treatment once the central nervous system is invaded as evidenced by the presence of the preparalytic stage. On the other hand, these apparent negative results on such a limited number of cases cannot be said to prove that the serum is valueless. Until the publication of these results it was the consensus of opinion that, while convalescent serum was of no avail in the paralytic stage, it was effectual if administered in the preparalytic stage. To many of us experienced in treating this disease, these published results were opposed to rather deep-seated impressions gained from bedside observations. The great trouble with most of us was that we had little experience with the preparalytic cases aside from those treated with serum. Indeed, our enthusiasm for the serum fanned the flame of the lay press propaganda, and impeded any attempt at checking our results. The clinician is now faced with controlled observations which conflict with an established impression gained from experience—always a difficult psychologic factor to overcome in the progress of medicine.

Isolated charts have been published pointing to a sudden drop in temperature following the administration of serum. All of us experienced in treating poliomyelitis have such charts in our record files, but we all know that these drops in temperature are not constantly

observed in early treated cases. Consequently, no composite charts have been published to establish this as a constantly observed phenomenon. In scarlet fever, on the other hand, the early use of convalescent serum gives a striking drop in temperature, and composite charts establishing this phenomenon have been published along with control composite charts. The difference is obvious, and the evidence is therefore of distinct value, as contrasted to the utter lack of results in any properly controlled series in poliomyelitis.

The question of administration of the serum is, of course, intimately associated with the problem of its evaluation. Indeed, it is only reasonable to assume that in attempting to combat a disease with any antitoxin the supply must be adequate in order to obtain results. Just what constitutes an adequate dose in a given case is as yet unknown, because we are not in a position to prove from comparative statistics or controlled clinical experiments that any dosage is actually efficacious. Therefore, the question of dosage, as well as the question of the best method of administering the dose, remains as a corollary subordinated to the question whether any serum yet produced is actually efficacious. As yet it is impossible to show from comparative statistics that the best results are achieved with the larger doses of convalescent serum, because no controls have been made in this respect. Furthermore, the same may be said regarding the different methods of administering convalescent serum. It has already been mentioned that animal experimentation merely offers us premises from which to speculate. The procuring of clinical proof is quite a different matter.

Under these perplexing conditions it is quite natural that the question should be raised regarding the statistical results obtained in general in the treatment of poliomyelitis. Up to the present time no compilation with any attempt at completeness has been put forward. The reason for this seeming neglect appears to lie in the fact that no final judgment from such a compilation could be achieved owing to the impossibility of incorporating in the tables the many factors which bring to bear a wide variety of influences on the results of the different observers. With a full realization of the dangers and pitfalls to be encountered, this presentation of compiled statistics from all available sources is submitted. It is worthy of note that in the great majority of instances the authors of the reports utilized in this compilation concluded from their individual results that their serum appeared to be of benefit. Much might be said in behalf of these positive conclusions, but there is also much to criticize in the evidence offered. Without professing to do justice to individual claims, this work aims merely to reduce the material to basic figures.

In making this compilation it was necessary to discard more reports than have been retained, because of inadequate data, or on account of reduplication of cases. In some instances a footnote to the effect that "some cases were treated" so and so leaves us in doubt as to how many, and, therefore, the figures could not be utilized for percentage purposes. Only such cases as afforded results which could conform to these tables

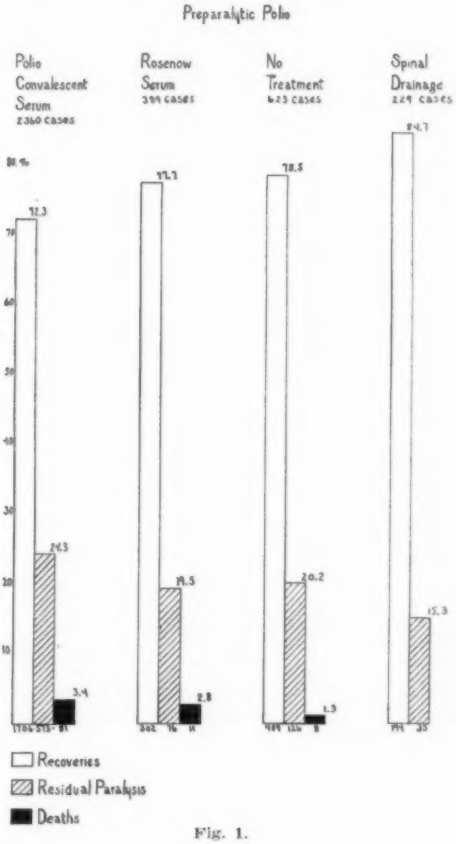

Fig. 1.

have been made use of. Some reports deal largely with the end-results as regards paralysis, and these are recorded so differently that it has been necessary to interpret degrees of paralysis for the purpose of adjusting the results to these tables.

In order to do justice to the material it has seemed best to give a protocol with all the sources, and to summarize by groups before tabulating. In this way the final figures given in the tables can be more readily

TABLE I

CASES THAT HAD THEIR FINAL RESULTS AS TO PARALYSIS STATED

PREPARALYTICS	PER CENT DIED	PER CENT SURVIVED	PER CENT RECOVERED	PER CENT RESIDUAL PARALYSIS	PER CENT UNCLASSIFIED	TOTAL CASES
Convalescent Serum	3.4	96.6	72.3	24.3	0	2360
Normal Human Serum	4.3	95.7	87.0	8.7	0	23
Rosenow Serum	2.8	97.2	77.7	19.5	0	389
Immune Animal Serum (Pettit, horse, goat, sheep)	3.7	96.3	81.5	14.8	0	27
Immune Animal and Convalescent Serum	15.4	84.6	77.0	7.6	0	13
Normal Horse Serum	0	100.0	68.7	31.3	0	16
Spinal Drainage Alone	0	100.0	84.7	15.3	0	229
Other Treatment	16.7	83.3	61.9	19.0	2.4	42
No Treatment Specified*	1.3	98.7	78.5	20.2	0	623
TOTAL	3.0	97.0	75.0	22.0	0.02	3722
PARALYZED						
Convalescent Serum	23.2	76.8	18.7	56.8	1.3	840
Normal Human Serum	14.8	85.2	11.1	74.1	0	54
Rosenow Serum	16.3	83.7	33.1	44.4	6.2	1166
Immune Animal	14.8	85.2	7.4	32.0	45.8	257
Immune Animal and Convalescent	25.0	75.0	0	75.0	0	12
Normal Horse	36.1	63.9	4.1	37.1	22.7	97
Spinal Drainage Alone	33.2	66.8	10.9	55.9	0	340
Other Treatment	9.5	90.5	14.3	76.2	0	21
No Treatment Specified*	17.2	82.8	6 9	70.2	5.7	2675
TOTAL	19.1	80.9	14.6	59.4	6.9	5462

*No serum used, including controls from all sources.

(SUMMARIES OF TABLE I)

TABLE II

CASES THAT HAD FINAL RESULTS AS TO PARALYSIS STATED

	TOTAL CASES	DIED	SURVIVED
Preparalytics	3722	111	3611
Paralyzed	5462	1043	4419
TOTAL	9184	1154	8030

TABLE III

	TOTAL SURVIVORS	RECOVERED	RESIDUAL PARALYSIS	UNCLASSIFIED
Preparalytics	3611	2780	830	1
Paralyzed	4419	796	3245	378
TOTAL	8030	3576	4075	379

analyzed and their significance can be more easily interpreted. It is of the utmost importance to note the number of cases from which any percentage figures are derived.

In the preparalytic group it becomes apparent that the larger the number treated by any method the more close the mortality percentage is to the mortality percentage for all preparalytics; namely, 3.1 per cent. It would thus appear to be obvious that the mortality in preparalytic cases is not appreciably affected by any treatment, so far as the total results indicate. As regards the percentage of residual paralyses in this group, it likewise becomes obvious that the variations above and below the final figure of 22.3 per cent are not significant except as to their tendency to conform fairly closely to this figure. The same may also be said of the recoveries under the different methods, all being remarkably near 74.6 per cent. Thus the three criteria on which the supposed efficacy of these methods are based offers nothing in the way of substantial evidence that the different methods have any constant appreciable value.

There are, of course, other criteria than the above. For instance, in the preparalytic cases treated with convalescent serum which subsequently developed paralysis ($62 + 573 + 81 = 716$) the mortality was only 11.3 per cent as compared with the mortality of 20.2 per cent for the total of all paralyzed cases with or without treatment. (Table VI.) However, in the preparalytic cases treated with Rosenow serum which subsequently developed paralysis ($3 + 76 = 79$) the mortality was 13.9 per cent. Taken individually one might comment favorably on the value of either serum by comparing either 11.3 or 13.9 with 20.2, but taken collectively the favorable impression is less impressive. Again, when one applies this same method of deduction to the still smaller group of preparalytics treated with spinal drainage alone which subsequently developed paralysis ($1 + 35 = 36$) and among whom there were no deaths at all, one is forced to the suggestion that there are factors favorable to recovery in the early treated cases quite independent of serum therapy.

In the paralyzed group the mortality per cent is of course higher than in the preparalytic group, but here the variations are actually no greater in comparison than in the preparalytic group, and the figures run sufficiently close in mortality, residual paralyses, and recoveries to indicate that no one method of treatment excels any other.

At this point it is appropriate to recall that it has always been difficult to judge the merits of serum therapy until a sufficient number of cases have been treated under diverse conditions to give weight to the results. The early figures[20] of antitoxin therapy in diphtheria are regarded as obviously misleading because the mortality from diphtheria

TABLE IV

PREPARALYTIC	TOTAL SURVIVING CASES	NO PARALYSIS	TEMPORARY PARALYSIS	UNCLASSIFIED COMPLETE RECOVERIES	PARALYZED	UNCLASSIFIED SURVIVALS	TOTAL CASES	DIED	%
Convalescent Serum	2306	1595	62	49	573	27	2390	84	3.5
Convalescent with Normal Horse Serum	3	3	0		0	0	3	0	0
Normal Human Serum	22	19	1		2	0	23	1	4.3
Rosenow Serum	378	299	3		76	0	389	11	2.8
Immune Animal Serum (Pettit, horse, goat, etc.)	26	20	2		4	0	27	1	3.7
Immune Animal and Convalescent Serum	11	5	5		1	0	13	2	15.4
Normal Horse Serum	16	11	0		5	6	16	0	0
No Serum (Spinal Drainage and other treatment)	264	219	1		43	1	271	7	2.5
No Treatment Specified	648	484	5		126	33	660	12	1.8
TOTAL	3674	2655	79	49	830	61	3792	118	3.1
PARALYZED									
Convalescent Serum	775		157		477	141	1048	273	26.0
Normal Human Serum	71		6		40	25	87	16	18.5
Rosenow Serum	976		386		518	72	1166	190	16.3
Immune Animal Serum	219		19		82	118	257	38	14.7
Immune Animal and Convalescent Serum	9		0		9	0	12	3	25.0
Normal Horse Serum	62		4		36	22	97	35	36.1
No Serum (Spinal Drainage and other treatment)	698		37		191	470	1061	363	34.2
No Treatment Specified	4573		240		1998	2335	5535	962	17.3
TOTAL	7383		849		3351	3183	9263	1880	20.2

(Summaries of Table IV)

Table V

	TOTAL SURVIVING CASES	RECOVERED	PARALYZED	UNCLASSIFIED
Preparalytic	3674	2783	830	61
Paralyzed	7383	849	3351	3183
TOTAL	11057	3632	4181	3244

Table VI

	TOTAL ALL CASES	DEATHS	PER CENT
Preparalytic	3792	118	3.1
Paralyzed	9263	1880	20.2
TOTAL	13055	1998	15.3

was falling from natural causes during this early period. It was not noted until much later that the mortality from scarlet fever was falling quite as rapidly at this time as was that of diphtheria, although no specific therapy was being used against scarlet fever. Furthermore, the greatest drop in diphtheria mortality as viewed on the usual charts printed in the textbooks appears to have taken place when the doses were so small as to be considered inadequate today. It is only at this later period, when many considerations can be carefully weighed, that one is able to evaluate diphtheria antitoxin. Furthermore, the first serious, clinically controlled hospital study of diphtheria antitoxin was not undertaken until 1918, and the results of this elaborate protocol as prepared by Bingel[21] were not favorable to antitoxin treatment. However, the negative results obtained from this single investigation have not altered the teaching of early and adequate antitoxin therapy in this disease, because the bulk of evidence supports this teaching. Nevertheless, it is well to present all the evidence in supporting any serum therapy from the standpoint of theory and practice, and to avoid unwarranted dogmatic assertions. Consequently, in poliomyelitis it is well to realize that our figures pertaining to serum therapy are still too meagre to serve as a final criterion, that the conditions under which its value is observed are even more complex than in diphtheria, and that it would be a serious mistake in the present state of our knowledge to abandon our efforts in this field.

It is to be distinctly understood that this work has been undertaken in order to answer a demand for comparative statistics on the subject. The value of this answer does not lie in any mathematical proof to the effect that serum therapy in poliomyelitis is useless, but rather in showing that

no positive proof can be adduced therefrom that one method is distinctly better than another. As such this compilation may serve as a basis for further investigation.

SUMMARY

1. Although we have tangible proof of the presence of specific immune bodies in the serum of convalescent poliomyelitis cases and in a high percentage of the sera obtained from normal adults as evidenced from laboratory experiments, there is no positive proof from this compilation of statistics or from controlled clinical experiments that such sera are efficacious after the preparalytic stage is once manifested.

2. The question of dosage and the question of administration of the dose cannot be answered until we have positive proof that the serum is efficacious.

3. The absence of positive proof from the material at hand should not deter us from further attempts to benefit cases by the use of antisera, merely because this material is as yet unsatisfactory owing to a variety of known and unknown factors which cannot be introduced with the figures.

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Protocols†

POLIO CONVALESCENT SERUM

PREPARALYTIC									PARALYZED						
AUTHORITY	TOTAL ALL CASES	NO PARALYSIS	TEMPORARY	SLIGHT	MODERATE	SEVERE	DIED	TOTAL PREPARALYTICS	UNCLASSIFIED	TEMPORARY	SLIGHT	MODERATE	SEVERE	DIED	TOTAL PARALYTICS
2	6									1	1	2		2	6
3	32	1						1		5	18			8	31
4	4	1						1				2	1	0	3
5	12	7						7		2				3	5
7	11			2				2		1	2	2		4	9
8	6										1	2	3		6
9a	4								2					2	4
9c	19								6					13	19
10	48									14		21	12	1	48
11	46	19	2	10	3	2	5	41		1	2			2	5
12	26	10	1	1			2	14		2	7	2		1	12
13	173	44	5	5				54		8		66		45	119
14	51	35		6	3	2	5	51							
15	27	3		1			1	5		13	4	3	1	1	22
16	48	5		3				8	19					21	40
17	15	6		1				7		1	5			6	8
24	19									5	14				19
23	Cases included under 15														
26	1	1						1							
29	12	4		1				5			6			1	7
30	43	16	3					19		6	7	4	2	5	24
31	106	37		55	8	5	1	106							
32	8									1			1	6	8
34	19	1						1		2	8			8	18
36	6			1							2			4	6
37	62	27		27	3	0	4	62							
				1											
38	54	27		19	2	2	3	54							
39	106	69		4				73		7	15			11	33
40	53								11	12	8	9	4	9	53
41	141	109		4		1	1	115		2	14	7	1	2	26
48	11									4	1	6			11
49	74	51		8	8		7	74							
50	74			27			3	30	29					15	44
51	43									14		17		12	43
52a	55	18	8		7			33		5		12		5	22
53	107	23	7	7			1	38	19					20	69
54	9	1	2					3		4		2			6
55	11	2	6					8					1	2	3
57	149	77	7	8	3	8	3	106		2	16	12	3	10	43
58	133	70	1	56	3	2	1	133							
60	54	49		5				54							
61	13	10		1				11			1		1		2
62	519	357		40*	102		20	519							
63	931	533		85	47		24	689		45	69*	81		47	242
64	97	31	20	8	3		3	65	25					7	32
	3438	1595	62	336	28	22	84	2390	141	157	135	45	30	273	1048
		49			187		Severity known					267		Severity unknown	

Unclassified 27

*Classified as "weakness"

†References to protocols follow protocols.

*Classified as "weakness"

No Treatment Specified

Authority	Total all cases	PREPARALYTIC: No paralysis	Temporary	Slight	Moderate	Severe	Died	Total prelytics	PARALYZED: Unclassified	Temporary	Slight	Moderate	Severe	Died	Total paralytics
1	4										1		3		4
6	1													1	1
11	33								3	19		8		3	33
14	3	2			1			3							
15	4									2			1	1	4
16	16	15		1				16							
17	29	24			5			29							
18	301								204					97	301
21	72								28	11		14		19	72
22	13	9		1	1		2	13							
23	710	59						59	1	43		488		119	651
24	246				32		4	36				170		40	210
27	12									5		5		2	12
28	1468								1063	56	35		36	50	228	1468
29	24	4						4				16		4	20
30	38									2		33		3	38
31	482									8		406		68	482
32	149								140					9	149
33	185	15						15				132		38	170
35	36	4						4				28		4	32
37	45								9	4	14		5	5	8	45
38	252								205						47	252
39	54									11		34			6	51
40	123									10	29	47	11		26	123
42	19								10						9	19
43	10									2	7				1	10
44	39											16		10	13	39
49	196	1						1			166				29	195
52a	12											11			1	12
52b	126								108						18	126
53	20	11	5		4			20								
54	43									1	37	2			3	43
56	2	2						2								
57	349	2						2		28	119	80	45	75	347
58	151	2						2	114		12	5	4	11	149
59	4									2	2				4
61	2	1						1			1				1
62	408	301		58*		45	4	408							
63	405	32		6*		5	2	45		33	111*		163	54	361
64	108													22	108
	6195	184	5	66	1	0	12	660	2335	210	368	175	129	962	5535

Unclassified 33
Severity unknown 59
*Classified as "weakness"

Severity unknown 1326
*Classified as "weakness"

Cases Without Serum Treatment

Authority	Total all cases	PREPARALYTIC: No paralysis	Temporary	Slight	Moderate	Severe	Died	Total prelytics	PARALYZED: Unclassified	Temporary	Slight	Moderate	Severe	Died	Total paralytics	
A. SPINAL DRAINAGE ALONE																
1	30									3	12	9		6	30	
20	507	177			29			206		32	32		130	107	301	
25	23	14	1		3			18		2		3			5	
32	9	2			3			5				4			4	
9a	43								26					17	43	
9b	156								135					21	156	
9c	328								207					121	328	Severe only
	1096	193	1		35		0	229	368	37	44	9	137	272	867	
B. OTHER TREATMENT																
8	2	1						1			1				1	Adrenalin chloride
9a	19								9					10	19	Adrenalin
9b	107				1		7	8	50					49	99	Adrenalin
9c	11								2					9	11	Adrenalin
9c	27								12					15	27	Autoinoculation
9c	5								2					3	5	Diph. antitox
34	20									3		15		2	20	Autohemic
42	10								5					5	10	Ephedrin salt
47	2										2				2	18% sod. chlor.
65	33	25		7*	1			33								Sterile milk
	236	26		7*	2		7	42	102	3	1	17		93	194	

*Classified as "slight weakness"

SPECIAL SERA

PREPARALYTIC									PARALYZED						
AUTHORITY	TOTAL ALL CASES	NO PARALYSIS	TEMPORARY	SLIGHT	MODERATE	SEVERE	DIED	TOTAL PREPARALYTICS	UNCLASSIFIED	TEMPORARY	SLIGHT	MODERATE	SEVERE	DIED	TOTAL PARALYTICS	
ROSENOW'S SERUM																
19	4									3	1				4	
21	259	59	1					60	14	129		37		19	199	
25	3	2						2			1				1	
28	1113	188		31	7	6	8	269	58	205	169	136	124	152	844	
					29											
29	13	1		1			1	4				8		1	9	
					1											
35	15	4						4			2	1	4	4	11	
44	148	45	2	1			2	50		49	19	6	10	14	98	
	1555	299	3	33	7	6	11	389	72	386	191	143	138	190	1166	
			Paralyzed 30								Paralyzed 46					
PETTIT SERUM																
32	8									1	1		3	3	8	
34	27									6		16		5	27	
46	1													1	1	
54	52	1			1			2		5	31	6	1	7	50	
59	19			2				2			9	3	2	3	17	+ normal blood
	107	1		2	1			4		12	41	9	6	19	103	
											Paralyzed 16					
NORMAL HORSE AND CONVALESCENT SERUM																
49	3	3						3								
OTHER IMMUNE ANIMAL SERUM																
18	159	13					1	14	118	3	3	3		18	145	horse
45	1	1						1								Pettit & monkey
52a	7	1	1					2		2		2		1	5	goat
52a	7		1		1		1	3				3		1	4	goat & conv.
52a	10	4	1		1			6		2		2			4	sheep
52a	13	5	4					9				4			4	sheep & conv.
54	5						1	1			1	1		2	4	Pettit & conv.
	202	24	7		2		3	36	118	7	4	4		22	166	
				Paralyzed								11				
												Paralyzed				
NORMAL ADULT SERUM																
6	3									2	1				3	Transfusion
13	43	9					1	10		4		24		5	33	
57	31	10	1	2				13			9	6		3	18	
64	33								25					8	33	
	110	19	1	2			1	23	25	6	10	6		16	87	
												24				
												Paralyzed				
NORMAL HORSE SERUM																
4	6	1						1		2	2	1			5	
9c	92								22	2		33		35	92	
49	15	10			5			15								
	113	11			5			16	22	4	2	34		35	97	

SUMMARIES OF PROTOCOL

POLIO CONVALESCENT SERUM

Total cases: 3438 with 357 deaths (10.3%)

Serum given in the preparalytic stage: 2390 with 84 deaths (3.5%)

Unclassified as to paralysis: 30 with 3 deaths

Of the remaining 2360 cases:

No paralysis at any time	**1595**	
Developed a temporary paralysis	**62**	
Either had none or temporary paralysis	**49**	
Completely recovered	**1706**	**(72.3%)**
Residual paralysis	**573**	**(24.3%)**
Died	**81**	**(3.4%)**
	2360	

Serum not given until paralysis was evident: 1048 with 273 deaths (26%)
End results of paralysis not classified 208 with 78 deaths
Of the remaining 840 cases:

Died	195 (23.2%)
Recovered	157 (18.7%)
Residual paralysis	477 (56.8%)
Unclassified	11 (1.3%)
	840

NORMAL ADULT SERUM
Total cases: 110 with 17 deaths (15.4%)
Serum given in the preparalytic stage: 23 with 1 death (4.3%)

No paralysis	19 (82.6%)
Temporary paralysis	1 (4.4%)
Recovered	20 (87.0%)
Slight residual paralysis	2 (8.7%)
Died	1 (4.3%)

Serum given after paralysis was evident: 87 with 16 deaths (18.5%)
Residual paralysis not noted 33 with 8 deaths
Of the remaining 54 cases:

Recovered		6 (11.1%)
Died		8 (14.8%)
Permanent paralysis		40 (74.1%)
Slight	6	
Moderate	10	
Some degree of residual paralysis	24	

NORMAL HORSE SERUM
Total cases: 113 with 35 deaths (30.9%)
Serum given in the preparalytic stage: 16 with no deaths

No paralysis	11 (68.7%)
Paralysis	5 (31.3%)

Serum given after paralysis was evident: 97 with 35 deaths (36.1%)

Recovered	4 (4.1%)
Paralyzed	36 (37.1%)
Survived but degree of residual paralysis not noted	22 (22.7%)
Died	35 (36.1%)

NORMAL HORSE SERUM AND CONVALESCENT SERUM (included on chart with convalescent serum series)
Three preparalytics: All recovered without paralysis

SPINAL DRAINAGE ALONE
Total cases: 1096 with 272 deaths (24.8%)
Drainage in preparalytic stage: 229 with no deaths

No paralysis	193 (84.3%)
Temporarily paralyzed	1 (0.4%)
Recovered	194 (84.7%)
Paralyzed	35 (15.3%)

Drainage begun after paralysis was evident: 867 with 272 deaths (31.3%)
Paralysis not classified 527 with 159 deaths
Of the remaining 340 cases:

Died	113 (33.2%)
Recovered	37 (10.9%)
Residual paralysis	190 (55.9%)

ROSENOW'S SERUM

Total cases: 1555 with 201 deaths (12.9%)

Serum given in preparalytic stage: 389 with 11 deaths (2.82%)	
No paralysis	299 (76.9%)
Temporary paralysis	3 (0.8%)
Recovered	302 (77.7%)
Paralyzed	76 (19.5%)
Serum given after paralysis was evident: 1166 with 190 deaths (16.3%)	
Recovered	386 (33.1%)
Residual paralysis	518 (44.4%)
Degree of residual paralysis not known	72 (6.2%)

PETTIT'S SERUM (IMMUNE HORSE)

Total cases: 107 with 19 deaths (17.7%)

Serum given in preparalytic stage: 4 with no deaths	
No paralysis	1 (25.0%)
Slight paralysis	2 (50.0%)
Moderate paralysis	1 (25.0%)
Serum given after paralysis was evident: 103 with 19 deaths (18.4%)	
Recovered	12 (11.7%)
Residual paralysis	72 (69.9%)

OTHER IMMUNE ANIMAL SERUM (Goat, horse, sheep, Pettit, and monkey)

Total cases: 177 with 20 deaths (11.3%)

Serum given in preparalytic stage: 23 with 1 death (4.3%)	
No paralysis	19 (82.6%)
Temporary paralysis	2 (8.7%)
Recovered	21 (91.3%)
Paralyzed	1 (4.4%)
Serum given after paralysis was evident: 154 with 19 deaths (12.4%)	
Residual paralysis unknown	118 (76.6%)
Recovered	7 (4.5%)
Paralyzed	10 (6.5%)

IMMUNE ANIMAL AND CONVALESCENT SERUM (Convalescent with goat, sheep, and Pettit sera)

Total cases: 25 with 5 deaths (20%)

Serum given in preparalytic stage: 13 with 2 deaths	(15.4%)
No paralysis	5 (38.5%)
Temporary paralysis	5 (38.5%)
Recovered	10 (77.0%)
Paralyzed	1 (7.6%)
Serum given after paralysis was evident: 12 with 3 deaths (25.0%)	
Paralyzed	9 (75.0%)

OTHER TREATMENT (Adrenalin, K. L. antitoxin, sterile milk, ephedrine salts, 18% sodium chloride, and autoinoculation)

Total cases: 236 with 98 deaths (41.5%)

Treatment in preparalytic stage: 42 with 7 deaths	(16.7%)
Recoveries	26 (61.9%)
Paralyzed	8 (19.0%)
Unknown	1 (2.4%)

(Of these 42 preparalytics, 33 were treated with sterile milk with no deaths)

No paralysis	25 (75.7%)
Some degree of paralysis	8 (24.3%)

Treatment after paralysis was evident: 194 with 91 deaths (46.9%)

Of the 21 cases classified:

Deaths	2 (9.5%)
Recovered	3 (14.3%)
Paralyzed	16 (76.2%)

NO TREATMENT SPECIFIED

Total cases: 6195 with 974 deaths (15.7%)

Preparalytic stage: 660 with 12 deaths (1.8%)

Unclassified: 37 with 4 deaths

Of the remaining 623 cases:

No paralysis	484 (77.7%)
Temporarily paralyzed	5 (0.8%)
Recoveries	489 (78.5%)
Permanently paralyzed	126 (20.2%)
Died	8 (1.3%)

Paralytic stage: 5535 with 962 deaths (17.3%)

Residual paralysis not classified: 2860 with 503 deaths

Of the remaining 2675 cases:

Recovered	184 (6.9%)
Residual paralysis	1877 (70.2%)
Died	459 (17.2%)
Results not classified	155 (5.7%)

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PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

Preliminary Report on the Treatment of Three Cases With Glycine

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MUSCULAR dystrophy, casually considered by most as a medical curiosity, is not so rare as it might seem. According to Hough,[1] its incidence is about 1 per cent of orthopedic cases. Anderson[2, 3] mentions that it is more common than usually thought, and that it might be wrongly diagnosed as flat feet, rickets, mild infantile paralysis or mental retardation.

The object of this paper is to present a report of thirty-eight cases of pseudohypertrophic muscular dystrophy found in Indianapolis hospitals with special regard to their treatment, and to present a preliminary report on three cases treated with glycine according to the methods of Milhorat, Technor and Thomas[4, 5] in the Leipzig Physiologisch-Chemisches Institut.

A summary of the cases is as follows:

Age period: 2 to 50 years.
Duration of illness: 1 to 14 years.
Sex: 1 female and 47 males.

Muscles involved:

Atrophy of arm muscles	19
Atrophy of leg muscles	13
Hypertrophy of arm muscles	11
Hypertrophy of leg muscles	21
Normal but weak muscles	2
No indications as to atrophy or hypertrophy	2
Knotty muscles	1
Arms not involved	9
Use of arms with difficulty	37
Loss of use of arms	2

Blood Wassermann: 40 negative.
40 Negative Wassermann.
8 Wassermann not reported.

Treatment with no Improvement:

Electrical reactions done	1
Not treated	23
Physical therapy	5
Suprarenal extract	3
Plaster bandage	1

From the Department of Pediatrics, Indiana University Medical School.

Strychnine	1
Pilocarpine and adrenalin	2
Insulin and carbohydrate diet (high)	6
Vaccine	3

Treatment with Improvement:

Glycine	3

History:

Hereditary	13
Following illness	4
Following injury	3

History on the remaining cases is not sufficient to determine whether or not the condition is hereditary.

Manifestation of Symptoms:

Gradual	8
Since birth	10

Psychometric Examination:

Feeblemindedness	16
Mentally alert	4
No psychometric	16
Average normal mental ability	2

Results:

44 Unimproved (Treated by methods listed above).
3 Improved (Treated with glycine).
(W. W.) Riley and City Hospital Case—Case 1.
(C. K.) Riley and City Hospital Case—Case 2.
(R. K.) Riley Hospital Case—Case 3.
1 Under observation.

We have reviewed and confirmed the work of Milhorat, Technor and Thomas, who have shown that patients with pseudohypertrophic muscular dystrophy show a creatinuria, even when maintained on creatine free diet. The normal subject excretes ingested creatine almost quantitatively (65-100%). The inability to retain ingested creatine is said to be in proportion to the severity of the disease.

Milhorat and his coworkers confirmed the findings of Gibson and Martin[6] on the study of creatine excretion and gelatin ingestion. Brand, Harris, Sandberg and Rueger[7] tried the effects of various amino acids on the excretion of creatine of patients with pseudohypertrophic muscular dystrophy, and found the administration of glycine caused the largest increase. These workers found that the ingestion of glycine (amino acetic acid) in these cases is followed by a large increase in the creatinuria. This significant relationship between glycine, a substance the normal subject can readily synthesize, and creatine, which has been demonstrated to play an important rôle in muscle function, suggested that the prolonged administration of this amino acidic acid might have an influence on the clinical and chemical course of the disease.

The earlier report showed that the daily ingestion of five grams of

glycine was followed by a definite rise in the creatinuria. The daily administration of 15 to 20 grams of glycine increased the daily excretion of creatine to 300-500 mg.

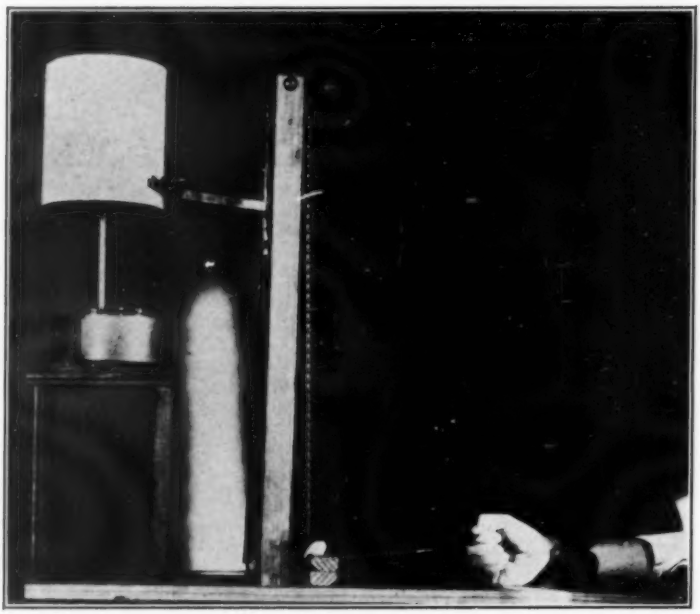

Fig. 1.

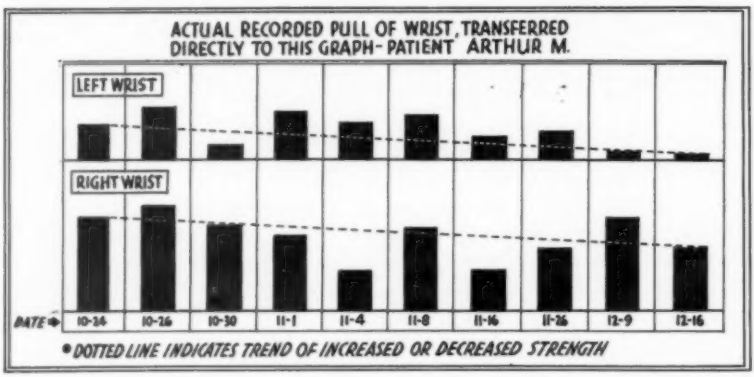

Fig. 2.

After a period of some weeks (depending on how advanced the case) the creatinuria begins to decrease despite the continuance of glycine until it falls to the former control level. In some cases this requires only two or three weeks.

Coincident with the increase in creatinuria, there is an improvement in the patient's ability to hold ingested creatine. These changes in the metabolism disappear in the course of a few weeks after the cessation of glycine ingestion, and return if the administration is again instituted.

The first symptoms of improvement are manifested by a curious feeling in the muscles which the patient described as a crawling, rumbling sensation. Following this, there is a disappearance of the sensation of fatigue. Muscles that had previously felt tired and heavy were reported to feel refreshed and lighter. Gradually the function of the involved muscle group is so improved that activity can be performed which had been impossible before administration of this drug.

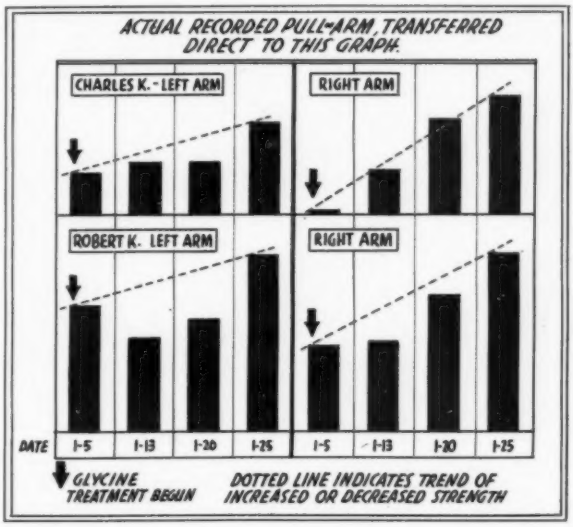

Fig. 4.

Independently of this case study, we secured the records of the muscular strength of three patients before, during, and after treatment with glycine. The recorded heights to which these patients were able to pull the lever on our ergographic-like instrument (Fig. 1), on separate dates, were recorded as a final graph (Figs. 2, 3, 4) which shows considerable variation and no improvement in the first case (Fig. 2); while in both the less advanced cases (Figs. 3 and 4), improvement was evident from the earliest records.

These individual records were dated as of the time when they were secured, and a summation of their curves directly transferred to the graph showing the actual height of the work done (Figs. 2, 3, 4).

Only one patient gave evidence of strange muscular sensation described by Milhorat.

CASE 1.—A. M., aged eleven years. Advanced case (Fig. 2). After thirty days of continuous treatment with glycine, (five grams three times a day) he was clinically no more improved than before treatment. However, complaints of fatigue were not so often heard from the patient after the continuous ingestion of glycine. It was noted that he was able to wind a Victrola crank a turn or so with his arm. Previous to this, he had been seen to use his mouth or jaw in the downpull of the crank. Our graph (Fig. 2) failed to show any objective improvement.

CASE 2.—C. K., aged twelve years. Moderately advanced case (Fig. 3). Under our observation since beginning of symptoms five years ago. Previously treated with adrenal cortex with no improvement. Patient was placed on 15 grams of glycine twice daily, and observed fourteen days. Our records (Fig. 3) show an

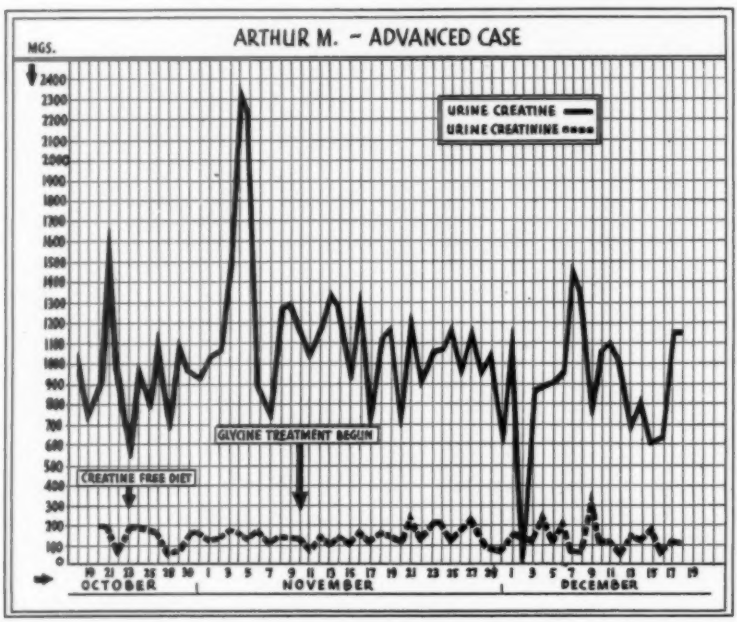

Fig. 5.

increase in the muscular strength of his arms. He was able to move his legs, which he had not been able to do previous to the last admission. There was no further complaint of pain in his legs upon passive motion of extremities. This patient had slight subjective feeling of "itching" or "crawling" feeling in his arm muscles.

CASE 3.—R. K., aged six years. An early case (Fig. 4). Brother of Case 2, patient was an ambulatory patient. This child was placed on glycine, 15 grams a day for fourteen days. Ergograph records taken showed evident improvement. His walking was much more steady, showed less waddling, and fewer falls. Definite objective improvement was noticed (Fig. 4).

Urine of these patients was collected as twenty-four-hour specimens (Figs. 5, 6, 7), according to the methods of Magee.[7, 8] Determinations of urine creatine and creatinine by Folin laboratory technic were made as soon after collection as possible. Magee says, "All reports in the

literature of creatinine excretion in muscular dystrophy have shown a marked fluctuation in the daily creatinine excretion, with the exception of a case reported by McCrudden and Sargent of a man over forty years of age." Figures (Fig. 5) of our first case were almost invari-

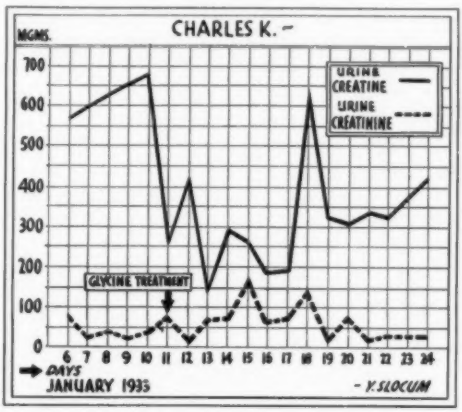

Fig. 6.

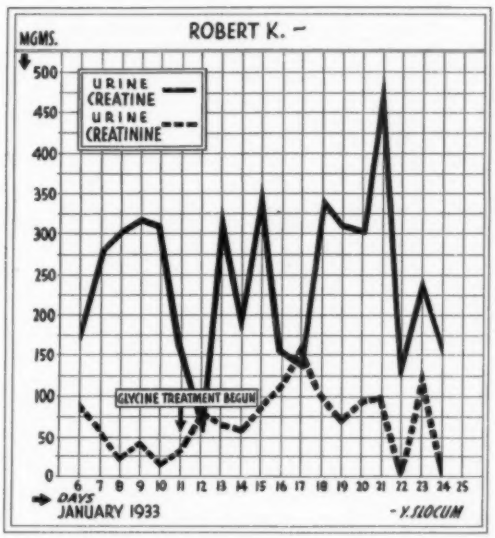

Fig. 7.

ably high but fluctuated constantly so that we were unable to report any change in creatinine excretion due to glycine ingestion on the patient's part. Fluctuation also seemed the rule in our less advanced cases (Figs. 6, 7) and our creatinine coefficient[9] was invariably low.

SUMMARY

1. Thirty-eight patients (48 hospitalizations) in Indianapolis hospitals with pseudohypertrophic muscular dystrophy are reported with emphasis on treatment.

2. Three cases were treated with glycine.

3. Two cases so treated showed improvement. One was only slightly improved.

4. Urinalyses for creatine confirm Magee's work.

CONCLUSION

The administration and study of glycine in cases of muscular dystrophy warrants further study. Studies are in progress as to the prolonged use of glycine, methods of administration, and the effects of other glycine-like compounds upon this disease.

NOTE: As pointed out by Quick (J. A. M. A. **99:** 57, 1932) glycine or glycocoll must not be confused with the photographic developer sold under the trade name "glycin" which is distinctly poisonous and according to a notice in the *Photographic Review* of September, 1932, published by the Eastman Kodak Co., has already resulted in an unfortunate occurrence.

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EPILEPSY. THE VALUE OF ENCEPHALOGRAPHY IN THE SELECTION OF PATIENTS FOR TREATMENT BY THE KETOGENIC DIET

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THE introduction of encephalography into the study of children suffering from convulsions has resulted in a better understanding of the gross structural changes that may be present in these patients. Many of these cases have shown "fixed" cerebral lesions[1, 2] as indicated by various degrees of dilatation, distortion, or displacement of the ventricular system, although occasionally unsuspected brain tumors or cysts have been demonstrated which has resulted in the immediate institution of proper therapy, whereas formerly only symptomatic measures would have been employed until such clinical manifestations developed that would have directed one's attention to the possibility of a cerebral neoplasm. Furthermore, encephalography has shown the futility of either surgical or medical treatment in those cases with widespread cerebral atrophy that may occur as a result of developmental defects, trauma, or infection.

In the conclusions of a previous paper[2] the following statement was made: "Probably one of the most important uses of encephalography will be its employment in the selection of suitable cases of epilepsy for treatment. One seems justified in assuming that if this procedure had been employed prior to the introduction of treatment for this disease an adequate explanation for some of the failures in the past would have been found." Since that communication, time has afforded the opportunity to evaluate this procedure both in the selection of suitable patients for treatment and in the selection of the form of therapy for the individual patient.

The purpose of this communication is to demonstrate the value of encephalography as an aid in the selection of patients for treatment by means of the ketogenic diet and also to point out its prognostic significance. However, before presenting the results of this study it seems advisable to briefly review some of the possible etiologic factors that may precipitate seizures (both petit mal and grand mal), and to consider some of the various forms of therapy that have been employed.

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At the present time seizures may be considered as occurring secondary to disturbances in cerebral function which may result from: (1) structural changes in the brain, or (2) to vasomotor changes or (3) to the state of hydration.[3] Based on these theories there have arisen various forms of therapy, each designed to meet the factor responsible for the precipitation of the seizure. From these procedures may be selected that form considered best suited to the individual patient. Briefly these forms of therapy are as follows:

(1) *Surgical Treatment.*—McClintic,[4] in carefully selected children with a clear-cut history of birth injury, has reported alleviation of symptoms by freeing the cerebral vessels from the influence of the vasoconstrictor nerves arising from the sympathetic ganglia of the upper thorax, neck and carotid bodies. This procedure presupposes that the attacks are due to angiospasm of the cerebral vessels. Foerster and Penfield[5] have obtained gratifying results in the surgical treatment of traumatic epilepsy, and by encephalography have presented evidence to show that the displacement of the ventricular system in this group of patients is due to cicatricial contracture which gradually draws one or both hemispheres toward the lesion.

(2) *Medical Treatment.*—This consists either in the employment of simple sedatives or in the establishment and maintenance of an adequate state of ketosis by employing a diet with sufficient protein, mineral and vitamin requirements but with a low carbohydrate and high fat content.[6] The mechanism by means of which the diet is effective is not clearly understood although it is thought that the altered water balance, due to the decreased carbohydrate metabolism,[7] may be the factor; i.e., dehydration. As an adjunct to the diet, and to further dehydration, the total fluid intake may be limited to any given amount. Fay,[8, 9, 10] and McQuarrie,[11, 12, 13] both supporting the theory of dehydration, although each explaining it by a different mechanism, have shown that during the period of negative water balance the tendency to seizure is diminished. Peterman,[14, 15] Helmholz,[16] and Talbot,[17, 18] have demonstrated the value of the ketogenic diet and have concluded that complete relief from the seizures may be obtained in about 33 per cent of the patients and improvement in an equal number.

Summarizing, then, one may say that certain patients suffering from epilepsy may respond to either medical or surgical intervention and that successful treatment largely depends on the proper selection of the patients for the different forms of therapy.

It is now recognized that many children with markedly dilated ventricular systems, with or without excessive amounts of air in the cerebral subarachnoid spaces, do not respond to any form of treatment except large doses of sedatives, whereas *selected* children with slight or moderate

enlargement or displacement of the ventricular system, such as seen after head injuries or mild birth injuries, may respond favorably to surgical attention. If these two groups; i.e., those that are not benefited and those that might respond to surgical intervention, are excluded, there then remains that large group of children with idiopathic epilepsy in which the encephalogram presents slight or no abnormalities.

By a study of the following cases we have endeavored to determine which of this last group of patients (i.e., those with slight or no abnormalities demonstrable by encephalography) will be benefited by ketosis.

The cases herein reported have been carefully studied and are patients suffering from idiopathic epilepsy. All children with a history of birth injury, head injury, infection, or blood dyscrasias of early infancy (i.e., hemorrhagic disease of the newly born) have been excluded. Each patient has been observed over a sufficient period of time to justify a definite opinion as to the efficiency of the form of treatment employed.

Twenty-nine patients have been studied by encephalography* and then treated by means of the ketogenic diet† with the results shown in Table I.

*Technic for encephalography: We have employed various forms of anesthesia for encephalography and have found that avertin alone (100 mg. per kilogram body weight), or in conjunction with light ether anesthesia to be quite satisfactory. The patient is then placed in an upright position and the needle is introduced in the usual manner. As soon as the cerebrospinal fluid is obtained, the pressure is recorded by an Ayer manometer. Throughout the procedure pressure determinations are made at frequent intervals and at no time is it allowed to be greater than that observed at the introduction of the needle.

By means of a glass syringe the fluid is slowly removed, usually in 5 c.c. amounts, and replaced with an equal volume of air. During the injection the use of a three-way stopcock has been found quite convenient as both the manometer and the syringe may be kept in position, and at the same time the fluid be allowed to drain. This obviates the danger of the needle being accidentally displaced from the spinal subarachnoid space by the frequent manipulation which would be necessary if the syringe and manometer were continuously being attached and detached.

As the fluid is being withdrawn and the air injected, the patient's head is moved from side to side and anteroposteriorly at frequent intervals. This procedure facilitates the drainage of the cerebrospinal fluid from the ventricles and subarachnoid spaces. Neither the amount of fluid removed nor the amount of air injected can be stated in categorical terms as they vary with each patient. No attempt is made to remove all of the cerebrospinal fluid by jugular compression, although as long as there is a free flow of fluid, air is injected volume for volume.

Following the injection of air the patient is taken directly to the roentgenologic department.

There he is placed on an ordinary roentgenographic table with Potter-Bucky diaphragm.

His head is rotated gently from side to side to equalize the air in the ventricles and then an exposure is made in the anteroposterior position. The head should be exactly centered and it is, of course, important in order to get good films that he is still subdued by the anesthetic.

The first film is developed immediately to see whether sufficient air is present to give good contrast and also to get some idea of its distribution. If the ventricles appear unequally filled or asymmetrical the anteroposterior procedure is repeated for a check. After that the patient is turned over to the prone position for posteroanterior and stereoscopic lateral films.

We have at no time found it necessary to use any special roentgenographic apparatus.

†The ketogenic diet, as described in detail by Talbot,[18] has been employed in all the patients studied. Ketosis has been established by presenting a diet in which the ketogenic ratio was greater than the antiketogenic; i.e., low carbohydrate and high fat. In the majority of the patients a ratio of 2½ :1 has proved satisfactory although occasionally it has been necessary to increase this to 3 or 3½ :1 before an adequate ketonemia could be established. The urine has been tested each morning and night by the parent for the presence of acetone and a detailed report made every two to three weeks. By insisting on this report we have been able to avoid possible mistakes in the diet and thereby maintain a constant state of ketosis. This detailed observation has been continued throughout the entire period of treatment.

TABLE I

CASE NO.	AGE AT ONSET YEARS	AGE AT TIME OF TREATMENT YEARS	TYPE OF SEIZURE	FREQUENCY OF SEIZURES	PSYCHOMETRIC EXAMINATION	ENCEPHALOGRAM	TREATMENT	DURATION OF TREATMENT	RESULTS
8193	3	10 5/12	Grand Mal	4-6 daily	Deterioration	Symmetrically and widely dilated ventricles	Ketogenic diet	2 mo.	No improvement
144756	2	3 3/12	Grand Mal	Several daily	Deterioration	Moderate dilatation of both lateral ventricles, particularly the left	Ketogenic diet	3 mo.	No improvement
146473	2	9	Grand Mal Petit Mal	Daily	Normal	Moderate dilatation of right ventricle	Ketogenic diet	5-6 mo.	No improvement
156286	2 5/12	3 7/12	Petit Mal of increasing severity	Daily	Deterioration	Moderate enlargement of both lateral ventricles	Ketogenic diet	4 mo.	No improvement
158069	2 8/12	5 9/12	Petit Mal	Daily	Inadequacy	Slight dilatation of both lateral ventricles	Ketogenic diet	5 mo.	No improvement
83734	1 9/12	8 3/12	Grand Mal	Gradually increasing; now has 2-3 per mo.		Slight dilatation of both lateral ventricles, particularly the left	Ketogenic diet	3 mo.	No improvement
136691	5 1/12	10 9/12	Grand Mal	Daily	Deterioration	Moderate dilatation of both lateral ventricles	Ketogenic diet	4 mo.	No improvement
145230	2 3/12	3 6/12	Petit Mal	Daily		Moderate enlargement of both lateral ventricles	Ketogenic diet	3-4 mo.	Diminution in frequency
138865	3	11 11/12	Grand Mal	Daily	Deterioration	Normal	Ketogenic diet	5 mo.	No improvement
133666	6 9/12	9	Grand Mal Petit Mal	Both daily		Normal	Ketogenic diet	? 4 mo.	No improvement
129531	10	10 10/12	Grand Mal	Daily		Normal	Ketogenic diet	1 mo.	No attacks while on the diet. Family discontinued it and the seizures recurred
64908	9 5/12	9 11/12	Grand Mal	1-2 each week	Deterioration	Normal	Ketogenic diet	4 mo.	No attacks since treatment instituted

TABLE I—CONT'D

CASE NO.	AGE AT ONSET YEARS	AGE AT TIME OF TREATMENT YEARS	TYPE OF SEIZURE	FREQUENCY OF SEIZURES	PSYCHOMETRIC EXAMINATION	ENCEPHALOGRAM	TREATMENT	DURATION OF TREATMENT	RESULTS
141078	1 5/12	2 2/12	Grand Mal	3-4 each mo. Gradually increasing	Normal	Normal	Ketogenic diet	18 mo.	No attacks during the 18 months of treatment. Now on a regular diet for 1 year without recurrences
151915	6 6/12	8	Grand Mal	Daily for past 3 mo.	Normal	Normal	Ketogenic diet	13 mo.	No attacks for first 6 months at which time she ate other food with loss of ketosis and recurrence of seizures. Diet resumed and for the past 7 months she has been free from symptoms
147516	3 10/12	4 10/12	Petit Mal Grand Mal	Petit Mal daily; seizures every 4-5 days		Normal	Ketogenic diet	12 mo.	Free for 6 months, then diet gradually altered to regular diet without return of symptoms
143291	2	6 10/12	Grand Mal Petit Mal	Petit Mal daily; gradually became Grand Mal. Daily seizures, varying 15-20		Normal	Ketogenic diet	8-10 mo.	As long as ketosis was maintained he had no symptoms. Finally gave up the diet and now has attacks daily
142658	10	13	Petit Mal Grand Mal	Daily	Deterioration	Normal	Ketogenic diet	10 mo.	Complete relief as long as ketosis could be maintained
82346	3	5	Grand Mal	3-4 attacks every few days	Deterioration	Normal	Ketogenic diet	3-4 mo.	Decrease in both severity and frequency
118903	3	7	Grand Mal Petit Mal	Daily	Deterioration	Normal	Ketogenic diet	Several periods of 3-4 mo. each	Complete relief as long as ketosis could be maintained

TABLE I—CONT'D

CASE NO.	AGE AT ONSET YEARS	AGE AT TIME OF TREATMENT YEARS	TYPE OF SEIZURE	FREQUENCY OF SEIZURES	PSYCHOMETRIC EXAMINATION	ENCEPHALOGRAM	TREATMENT	DURATION OF TREATMENT	RESULTS
116808	3	6 9/12	Grand Mal	Daily		Normal	Ketogenic diet	Various periods	Complete relief as long as ketosis could be maintained
117273	3 8/12	3 9/12	Grand Mal	Every other day		Normal	Ketogenic diet	10 mo.	At end of 6 months diet was gradually restored to a normal one without recurrence of symptoms
125383	2 8/12	3 2/12	Grand Mal	4-5 each week		Normal	Ketogenic diet	12 mo.	Three attacks during the first 5 months of treatment and then none during next 7 months. Now on regular diet and symptoms have not recurred
128873	3	5	Petit Mal Grand Mal	Numerous seizures daily		Normal	Ketogenic diet	6 mo.	Patient still on diet. Marked reduction in both frequency and severity. Definite improvement
150541	7 10/12	9 4/12	Grand Mal	8-10 per month	Normal	Normal	Ketogenic diet	Several periods of 1-2 mo. each	Complete relief as long as ketosis was maintained. Diet was finally discontinued and patient now has convulsions every few days
167408	11	3 3/12	Petit Mal changing to Grand Mal	3-4 seizures every few days	Normal	Normal	Ketogenic diet	3 mo.	Less frequent and less severe; now occur only at night.
158984	5	7	Grand Mal gradually increasing in frequency	3-4 seizures every 2-3 days	Normal	Normal	Ketogenic diet	10 mo.	1-2 seizures every 4-5 weeks and much less severe
164251	3/12	1 9/12	Grand Mal	3-4 each week	Normal	Normal	Ketogenic diet	1 mo.	No further seizures
166095	6	6 6/12	Grand Mal	15-20 per day every 4-6 days	Deterioration	Normal	Ketogenic diet	1 mo.	Attacks less frequent and much less severe
163180	3	3 4/12	Petit Mal	Every 2-3 days	Questionable	Normal	Ketogenic diet	1 mo.	Complete relief as long as ketosis is maintained

SUMMARY OF TABLE

(1) 14 patients with *normal* encephalograms responded by complete cessation of attacks.

(2) 5 patients with *normal* encephalograms responded by a diminution in number and severity of attacks.

(3) 2 patients with *normal* encephalograms failed to show any improvement.

(4) no patients with *abnormal* encephalograms responded by complete cessation of attacks.

(5) 1 patient with *abnormal* encephalograms responded by a diminished number of attacks.

(6) 7 patients with *abnormal* encephalograms failed to show any improvement.

CONCLUSIONS

(1) Twenty-nine children suffering from idiopathic epilepsy were subjected to encephalography prior to the institution of the ketogenic diet.

(2) Nineteen or 90.1 per cent of the children with *normal* encephalograms responded favorably and 2 or 10 per cent unfavorably.

(3) One, or 12 per cent, of the children with *abnormal* encephalograms responded favorably and 7, or 88 per cent, unfavorably.

(4) Encephalography offers a method by means of which suitable patients may be selected for the dietary form of treatment of epilepsy.

(5) Encephalography is of definite prognostic value in the treatment of epilepsy.

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THE BLOOD PICTURE IN THE EARLY STAGES OF PERTUSSIS

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FRÖLICH,[1] in 1897, was first to observe a high leucocytosis, with a high percentage of lymphocytes, in the third and fourth weeks of pertussis. He considered the leucocytosis as a possible sign for differentiation of pertussis from other diseases with a cough. He underestimated, however, the importance of the high percentage of lymphocytes, attributing it to the young age of his patients.

Meunier,[2] in 1898, called attention to the fact that the leucocytosis in pertussis is higher than in other afebrile diseases. In his experience, the leucocytosis appears at the onset of the spasmodic cough, and disappears with the end of the paroxysms. The leucocytosis was found to be due to the increase in the number of lymphocytes, although the number of other white blood cells was also increased.

Cabot,[3] in 1901, used the term "lymphocytosis" to emphasize that in pertussis the leucocytosis was due to an increase in the number of lymphocytes.

Crombie,[4] in 1908, found that the increase in the number of white blood cells was more pronounced in the cases of pertussis with severe and numerous paroxysms. This view is not shared by some of the later authors.

There is a considerable difference of opinion among the investigators in regard to the time of appearance of leucocytosis and lymphocytosis in the course of pertussis.

Since Wanstall[5] who, in 1903, had observed an increase in the percentage of lymphocytes before the onset of the spasmodic cough, a large number of authors reported that the characteristic blood picture appears already in the catarrhal stage of pertussis. This group of authors includes Wanstall, Ashby,[6] Churchill,[7] Barach,[8] Crombie, Schneider,[9] Cozzolino,[10] Heiman,[11] Ziegler[12] and Leitner.[13]

On the other hand, a number of authors hold that the typical blood picture appears only at the onset of the paroxysmal cough (Frölich; Meunier; Lasch, Fischer and Miemitz[14]; Sauer and Hambrecht[15]; Finkelstein[16]; Knöpfelmacher[17]; Holt and Howland[18]).

Extremely high leucocytosis, with a high percentage of lymphocytes, was seen in a number of cases with complications, usually with broncho-

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pneumonia (Cabot, Reiche,[19] Leitner, Seitz,[20] Bourne and Scott,[21] Mitchell and Friedman[22]). The highest total number of white blood cells reported was 233,600 cells per 1 cu. mm.[22] Many of the cases with extremely high total white cell counts were fatal. A very high leucocytosis may, however, be observed in cases without complications (84,000 in a case of Leitner's; 213,330 in the case of Abt[23]).

Pyogenic infections (Lasch et al.; Reiche) and bronchopneumonia do not usually change essentially the already established pertussis blood picture. Only a few authors mention a high percentage of neutrophils in pertussis with complications (Ziegler, in varicella during pertussis; Austrian,[24] in pneumonia).

The majority of authors hold that a *relative* lymphocytosis is diagnostic of pertussis, some even omitting the total leucocyte count in the examination of the suspicious cases (Wanstall, Heiman). Several observers pointed out, however, that an *absolute* lymphocytosis is an earlier and a more constant occurrence than the relative lymphocytosis (Ziegler, Lasch et al., Hillenberg[25]).

Carrière[26] and Thiemann[27] reported a high percentage of neutrophils in pertussis.

In a recent observation, Sauer and Hambrecht brought out the occurrence of leucopenia in the initial and terminal stages of pertussis.

In regard to the diagnostic significance of the blood picture in pertussis there is a wide range of opinion. All authors agree that pertussis is the only disease, except lymphatic leucemia, that may cause a high leucocytosis with a high percentage of lymphocytes. Those authors who observed the characteristic blood picture in the catarrhal stage consider the blood count as an important aid in the early diagnosis of pertussis (if cultures for the bacillus Bordet-Gengoult cannot be made). Baar and Stransky,[28] while not finding the lymphocytosis a constant feature of pertussis, consider the blood picture as an aid in the diagnosis of pertussis in nurslings. Finkelstein, on the other hand, is very skeptical as to the aid that may be derived from the blood picture for the early diagnosis of pertussis, because in his experience the lymphocytosis appears only in the third or in the fourth week of the disease. A more moderate opinion is expressed by Schmal, Schmidt and Serebrijski.[30] They consider that leucocytosis with a relative lymphocytosis is very often observed in pertussis, and that each suspicious case which shows these blood changes must be regarded as pertussis; the absence of leucocytosis and lymphocytosis should not, however, be a contraindication to a diagnosis of pertussis. McGee,[31] in observing 64 children suspected as early cases of pertussis, could diagnose the disease in 13 days with the aid of the blood picture, and in 25.5 days, if he waited till the appearance of the whoop.

Cozzolino, and Paolucci[32] consider that leucocytosis and lymphocytosis may persist in the blood picture after the disappearance of infectiousness.

While making blood counts twice a week, over a period of many months, on a number of children inoculated with the bacillus Calmette-Guérin, and on normal controls, we had a rare opportunity to observe the hematologic picture of five children for weeks before they contracted pertussis, and at the beginning of this disease. We could thus estab-

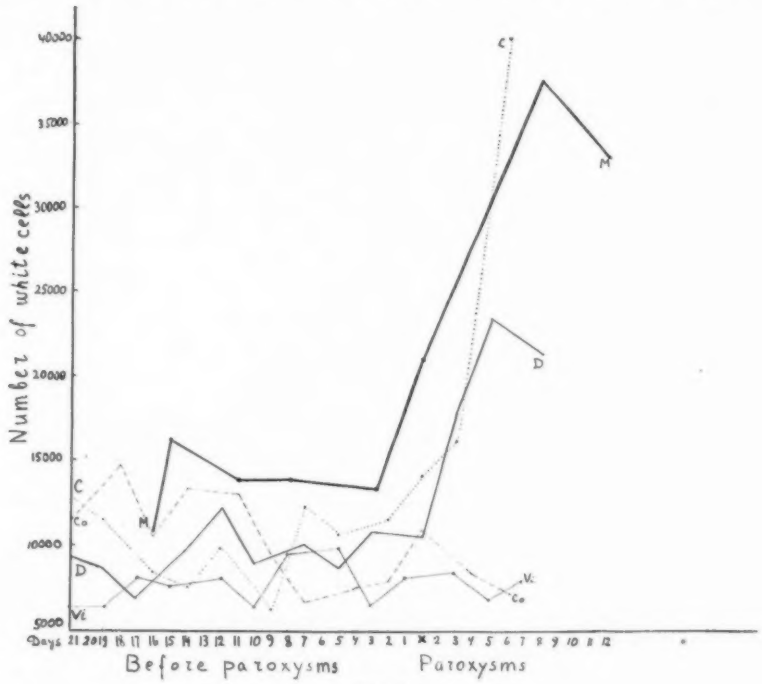

Fig. 1.

lish the range of normal hematologic variations for each child and compare his blood picture at the beginning of pertussis with his own blood picture under more or less normal circumstances.

The blood counts were made between 10 and 11 A.M. The curves include the blood counts for 21 days (or for 16 days in one case) before the appearance of the spasmodic cough.

In the catarrhal stage none of the children showed any leucocytosis above the usual figures for that child; the percentage and the absolute number of lymphocytes in four of them did not rise above some of the higher figures observed before pertussis (Fig. 1).

Two cases were diagnosed clinically as pertussis, and were removed to a hospital for communicable diseases, without showing any hematologic changes; no blood counts were made on these children in that hospital, so that their further hematologic history is unknown. Clinically one was a moderately severe case (Co., five months old); the other case, Vi., one year and six months old, was considered as a severe case of pertussis.

In two cases, after a normal hematologic picture during the catarrhal stage, the total number of white blood cells increased abruptly with the beginning of the paroxysmal cough. In both cases the increase in the

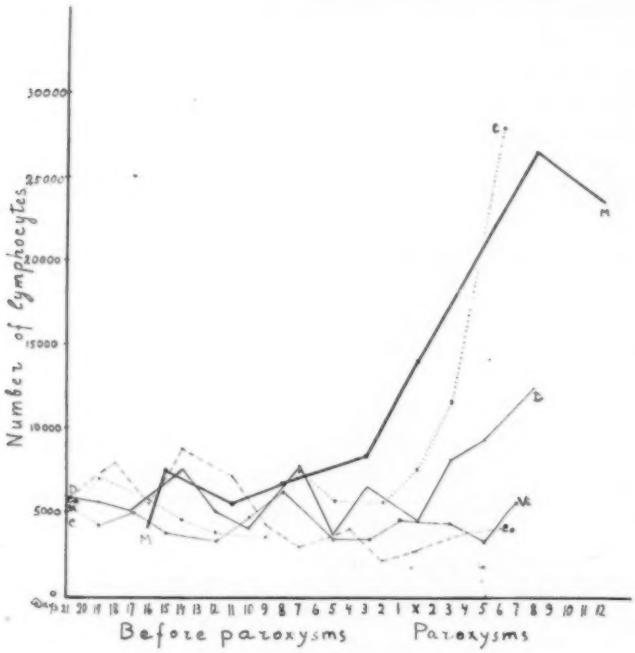

Fig. 2.

number of white cells was due to the increase in the *number of lymphocytes*. The percentage of lymphocytes was also increased, but was not so striking as the increase in the absolute number of lymphocytes (compare the lymphocyte curve of patient D. plotted in absolute figures and in percentage).

Both patients with high lymphocytosis, Case C., aged two years and three months, and Case D., one year old, had a mild form of pertussis (Fig. 2).

In one case (M., three months old) a relative and absolute lymphocytosis became evident at the end of the catarrhal stage. This child had a severe form of pertussis, with a febrile bronchitis. With the tempera-

ture 104° F. his blood picture showed 65,000 W.B.C. and 82 per cent, or 53,000 lymphocytes; with the diminution of the clinical signs, the total number of white blood cells, and the number and percentage of lymphocytes, showed a considerable decrease.

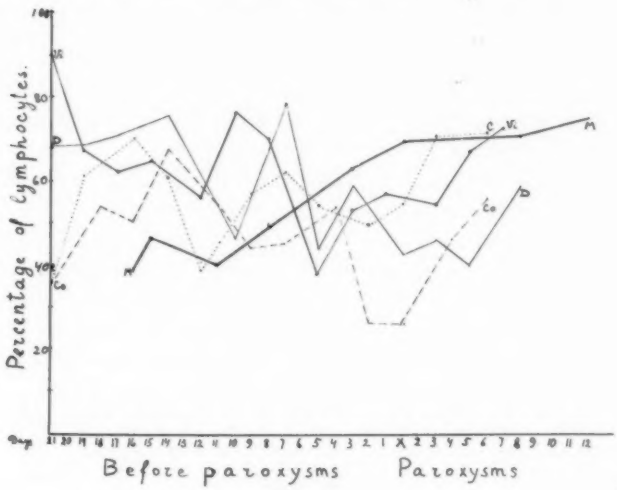

Fig. 3.

CASE M. BLOOD PICTURE DURING PERTUSSIS

DATE	TOTAL W.B.C.	LYMPH %	LYMPH NO.	NEUTR. %	NEUTR. NO.	MONO. %	E %	B %	REMARKS
8/12	10600	38.5	4081	50.0	5300	10.0	1.5		
8/13	16100*	46.0	7406	43.0	6923	8.0	1.0		Türk c. 2%
8/17	13700	40.0	5480	54.0	7398	3.0	3.0		
8/20	13700	48.5	6644	39.0	5343	9.0	3.0	0.5	
8/25	13300	63.0	8379	26.5	3524	5.5	3.5		Türk c. 1.5% Moist cough
8/28	21000	69.0	14490	24.0	5040	2.5	3.5		Türk c. 1% Spasmod. cough
9/ 4	37400	71.0	26554	23.0	8602	2.5	3.0	2.0	Spasmod. cough
9/ 8	33000	75.0	24750	22.0	7260	1.0	2.0		Spasmod. cough
9/10	65700	82.0	53874	16.0	10512		1.5	0.5	Temp. 104° Râles
9/14	24500	72.0	17640	24.0	5880	2.5		0.5	Rieder c. 1% Spasmod. cough
9/16	24700	70.5	17413	20.5	5063	7.0	0.5		Rieder c. 1% Spasmod. cough
9/22	18900	52.0	9828	40.0	7560	5.0	3.0		Spasmod. cough

*On this day of a heat spell several babies in the ward, under similar hematologic observation, showed total white blood cell counts up to 17,000, with lymphocytes up to 67 per cent.

As seen from the above figures, while the percentage of lymphocytes increases, the percentage of neutrophils diminishes. Such observations have led several authors to make a statement that "the number of lymphocytes in pertussis increases *at the expense* of the number of

neutrophils." However, the absolute number of neutrophils in this case shows no decrease (except for one day), and at times showed a definite increase. Calculations for absolute number of neutrophils made from the figures on several pertussis cases from the article of Leitner also showed that a low percentage of neutrophils may be co-existent with an actual increase of their number in 1 cu. mm. of blood.

SUMMARY

Although the number of cases observed at the beginning of pertussis is small, some conclusions can be made:

1. In the majority of cases no marked increase is observed in the total number of white blood cells or in the percentage of lymphocytes during the catarrhal stage of pertussis. These changes were observed only in the youngest child of this series (age of 3 months).

2. An abrupt increase in the total number of white blood cells, with an increase in the percentage and absolute number of lymphocytes, occurs in a number of cases with the beginning of the spasmodic cough. The increase in the *total* number of lymphocytes is more striking than the increase in the percentage of these cells.

3. The number of lymphocytes in 1 cu. mm. remains high during febrile bronchitis complicating pertussis.

4. While a high lymphocyte count is characteristic for pertussis and should be considered a diagnostic sign, when present, some cases may reach the paroxysmal stage without any leucocytosis, or a relative or absolute lymphocytosis.

5. Although the percentage of neutrophils in pertussis diminishes with the appearance of lymphocytosis, the absolute number of these cells does not drop, and may show an increase.

6. Absolute figures for various blood cells, together with the percentage of these cells, give a more valuable hematologic picture than the percentage figures alone.

I wish to thank Dr. Charles Hendee Smith for the permission to refer here to a case observed in the babies' ward at Bellevue Hospital.

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ANTIQUES OF PEDIATRIC INTEREST

T. G. H. Drake, M.B., F.R.C.P.(C)

HUGH SMITH in *Letters to Married Women on Nursing and the Management of Children*, 6th Edition, London, 1792, stated that "the infant body is by nature designed to receive only a liquid nourishment." He recommended whole cow's milk, skimmed or diluted with water if too creamy, and had no objections to a small quantity of Lisbon sugar being mixed with it, particularly if the child were costive. "Besides, to obtain milk from the breast, Nature wisely obliges

Hugh Smith's feeding pot, cream pottery, circa 1800, height 12 cm.

them to earn their nourishment by the labour of drawing it. There is nothing therefore wanting, I hope, to complete our system, but a contrivance to supply the place of the nipple, that the child may still labour to obtain its support; which alone will greatly prevent the error in quantity.

"Since this book made its first appearance, I have contrived a milk-pot for my own nursery upon the above principles; it appears to my family and to many of my patients, preferable to those now in use, and may probably be still further improved. For the satisfaction of my read-

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ers, I shall give a description of it. This pot is somewhat in form like an urn; it contains a little more than a quarter of a pint; its handle, and neck or spout, are not unlike those of a coffeepot, except that the neck of this arises from the very bottom of the pot, and is very small; in short, it is upon the same principle as those gravy-pots which separate the gravy from the oily fat. The end of the spout is a little raised, and forms a roundish knob, somewhat in appearance like a small heart; this is perforated by three or four small holes; a piece of fine rag is tied loosely over it, which serves the child to play with instead of the nipple, and through which, by the infant's sucking, the milk is constantly strained. The child is equally satisfied as it would be with the breast; it never wets him in the least; he is obliged to labour for every drop he receives, in the same manner as when at the breast; and, greatly in recommendation of this contrivance, the nurses confess it is more convenient than a boat, and that it saves a great deal of trouble in the feeding of an infant; which is the greatest security to parents, that their servants will use it, when they themselves are not present.

"The model of this milk-pot is left with Mr. Morrison, at the Three Kings, in Cheapside, for the benefit of the public. The milk-pots are now also made in the Queen's ware, in order that the poor may be accommodated: any person, therefore, at a very trifling expense, may be convinced of their utility by making the experiment."

Hugh Smith's feeding principles, and his feeding pot, were looked upon with great favor by Michael Underwood, who stated in his *Treatise on the Diseases of Children*, 1784, that "the boat, the spoon, and the horn, are in no wise comparable to the pot. The long spout rising from the bottom, and pierced only with a few small holes at the end, which is to be covered with a piece of vellum, or parchment, which, being left loose a little way over the spout, is soft and pleasant to the child's mouth, and is nearly as acceptable to many children as the breast, as I have often been a witness. This manner of feeding is not only pleasant to the child, but very convenient to the nurse, and the food equally at hand in the night as the day, being easily kept warm by a lamp, or even in the bed."

In the 1811 edition, in reply to a critic, Underwood wrote: "The objection to this mode of feeding, made by a writer at Dover, that the pot may often be left foul, and therefore the food become sour, appears to me to be very far-fetched; since if nurses are not to be depended upon in matters of cleanliness, and the sweetness of the food they are to administer, we can trust them in nothing."

Critical Review

SURGICAL PEDIATRICS

HERBERT E. COE, M.D., SEATTLE

THE subject of this review is phrased designedly to emphasize the necessity of a pediatric attitude of mind on the part of any one who carries out surgical procedures upon infants or children. The treatment of surgical conditions in children is not merely an adjustment of surgical principles and technic to a small scale. The child, as so frequently brought out in the reports of the White House Conference on Child Health and Protection, is a definite clinical entity, and the surgical problems are as definitely dependent upon the peculiar reactions and conditions of that period as are the medical. John Lovett Morse repeatedly emphasized this point in his classes by the statement that "a child is not a little man," and Barrington-Ward touches upon it when he says in reference to abdominal surgery in children "the adult may be safely treated as a child but the converse may lead to disaster." The constant evaluation of the surgery of childhood by reference to the surgery of adults is as illogical as would be the estimation of the diet of infancy and childhood by reference to the requirements of middle age.

The problems of surgery in adults are to a great extent those incidental to the removal of diseased or worn-out parts, and discussions in most surgical gatherings are focused upon malignancies, gallbladders, gastroenterostomies and other conditions encountered upon the western slope of life.

Our surgical reviews[1] pay scant attention to children and only recently[2] is our surgical literature beginning to follow the lead of the English and French[3, 4] in their recognition of the conditions peculiar to that period.

The great surgical advances of the past have been made in entering supposedly inaccessible or forbidden regions of the body, in the excision of organs, and in the development and refinement of technic. Recently, however, there has been a distinct trend toward physiologic surgery as typified by the broadening interest in surgery of the sympathetic nervous system, reconstructive surgery, Coffey's work upon ureteral implantation, and the like. At no period of life are physiologic processes more active than during infancy and childhood; at no period is the rate of development more rapid, and surgery of this period is, in the highest degree, physiologic and developmental surgery. The pediatrician is constantly thinking in terms of these conditions and if the surgery of infancy and childhood is to be most effective, it must approach its problems by way of pediatric thought and reasoning rather than by the cerebral pathways of the older surgery; it must be surgical pediatrics rather than pediatric surgery. This method of approach will, in the main, be easier for the general prac-

titioner with his constant subconscious adjustment to various personalities and conditions and the high proportion of infants and children who come under his care than for the general surgeon with an average of 80 per cent to 95 per cent adult work. On the other hand, the delicacy of the tissues, the narrow zone of safety, and the necessity for careful estimation of resistance call for surgical skill and judgment of the highest order.

Unquestionably many of the disagreeable childhood impressions and fears of the profession are associated with anesthetics. It is, perhaps, idle to speculate upon the subtle influences of such experiences but they may well be a factor in forming a reluctance to employ a physician in later life, or delay in calling one, or in the decision to turn to one of the cults. Experience with children who have had several operations brings out the fact that they object not so much to the postoperative discomfort and restriction as to the anesthetic with its feeling of suffocation and the forcible restraint.

In the literature of the past three or four years there have appeared approximately 1000 articles upon basal anesthesia, the earlier ones reporting the intravenous use of the barbiturates and the more recent ones the rectal use of tribromethyl alcohol under the trade name of avertin.[1, 6, 7] Many of these mention especially the prevention of psychic shock and the amnesia[6] which practically obliterates memory of the anesthetic, operation, and postoperative period.

Opinions regarding the use of avertin vary, some writers[6] stating that supplemental ether is synergistic, that the residue should be washed out after the operation and oil instilled, and that cases should be carefully selected; while others[9, 7] believe that it is suitable for a rather wide range of conditions, and that the combination is less toxic than either of the two drugs alone. Untoward reactions[10] are rare, a sharp but small drop in blood pressure resulting from too rapid injection, and cyanosis and cardiac or respiratory depression during anesthesia having been reported. Contraindications[7, 10] are liver or kidney dysfunction, rectal irritation, dehydration, debility, myxedema, and advanced tuberculosis. The supplemental anesthetic should be administered by a skilled anesthetist who should be prepared to combat complications by the use of an air way, by carbon dioxide inhalations, caffeine, atropine or ephedrine. Opinions differ as to the use of adrenalin. There is also considerable variation in the dosage advised, the range being from 60 to 120 mg. per kilo. Preliminary medication is optional. The solution must be prepared exactly according to directions, any marked variation in temperature or reaction resulting in the production of irritant substances and reduction in anesthetic effect.

Postoperative nausea and vomiting are noticeably reduced.

The necessity for postoperative bowel irrigation would seem problematical as 80 per cent of the drug is absorbed within twenty minutes and 95 per cent in two hours. The injection should be done slowly, ten minutes being a minimum, and the patient should not be transferred to the operating room in less than twenty minutes.

If used carefully avertin is a welcome addition to our resources, not only from the point of view of the patient but almost equally for its psychologic effect upon parents.

Although spinal anesthesia is reported favorably and at great length for adults there is a noticeable dearth and vagueness of reports upon its use in children. Its value is most outstanding where there is necessity for complete relaxation of the abdominal wall and bowel, as in intussusception, volvulus and ileus.[12] It stimulates peristalsis by temporarily paralyzing the brake mechanism of the intestine. Junkin[13] gives an excellent table of dosage for the use of novocaine in infants and children, citing cases from two weeks to seventeen years of age. Fairly large doses of preliminary opiates are used and occasional nausea and vomiting are noted during the operation. Whatever fall in blood pressure may occur is controlled by hyperventilation by carbon dioxide inhalations.

Spinal anesthesia carries with it certain psychic effects and except in cases where the physiologic action is paramount, patients should be chosen with careful attention to this factor. It is not as desirable as general anesthesia for ordinary use in children.

The absolute necessity of sufficient fluid for the proper functioning of the human body will bear frequent repetition. This complex cellular chemical workshop is easily thrown out of balance by dehydration[14] and at no period of life are the demands of the cells for fluid more acute and insistent than during the rapid growth of infancy and childhood. The maintenance of heat and fluid reserve is fundamental in the treatment of surgical conditions. The problem of supplying fluid in the infant is complicated by the factor of lack of cooperation, and when it is realized that there may easily be a loss of a pound of fluid a day it becomes evident that a condition of dehydration incompatible with life may soon develop.

The absorption of fluid is a normal physiologic function of the colon and this route has a deserved popularity. The amount of absorption of various solutions,[15, 16] however, has been open to question. It has been contended that the entire amount of glucose introduced may be recovered in bowel washings, the water only being absorbed. An attempt has been made to meet this condition by using hypotonic solutions, such as 1 per cent glucose either alone or in combination with ½ per cent sodium bicarbonate. Carefully controlled experiments, however, have apparently proved that the amount of alkali or carbohydrate absorbed by the colon is practically negligible. The absorption of water from the injected solution soon raises its concentration to a point where it becomes isotonic or even hypertonic, in which case it is either of no value or may actually withdraw water into the colon. The ileum, however, absorbs carbohydrate readily and if the solution passes an incompetent ileocecal valve it is utilized. Also in case of deficient blood sugar the colon absorbs carbohydrate nearly as readily as the ileum. The first of these conditions is variable and beyond the possibility of practical determination, and the second rarely obtains, so that it may be stated with reasonable finality that the amount of glucose absorbed from solutions in the colon is too small and variable to be of practical therapeutic value.

The intravenous method of administering solutions is so generally accepted that it need only be mentioned. In cases of extreme dehydration or loss of chlorides from vomiting, continuous intravenous injection of normal saline is often a life-saving measure. The rate of flow is adjusted to the degree of dehydration, being governed by the

quality and rate of the pulse, care being taken to avoid any evidence of respiratory or cardiac distress and the solution being allowed to flow continuously for three to six hours at a time. Glucose, either with or without insulin, may be added when carbohydrates are needed to combat acidosis or to supply nourishment.

For the treatment of postoperative abdominal distention[17] the intravenous administration of saline and glucose supplemented by diathermy to the abdomen is recommended. The marked relief following passage of great amounts of flatus almost immediately after the intravenous introduction of 100 to 500 c.c. of 3 per cent glucose is often quite spectacular.

When other routes of fluid administration are either contraindicated or inconvenient, the intraperitoneal[18] method may be used. The injection is usually made in the midline just below the umbilicus, but when rather large amounts are to be used there is less danger of leakage if the needle passes through the inner or outer edge of the rectus. Penetration through the middle of the rectus may injure the blood or nerve supply. The more enthusiastic advocates of intraperitoneal injections refer to the ease of introducing large quantities, the rapid absorption, the lack of strain on the circulation, the short time required and the ease of repetition. Ten to 15 c.c. per pound of body weight may be given, stopping upon the first sign of respiratory embarrassment. It is claimed that a great variety of solutions and food can be easily given; saline and Ringer's solution, 5 per cent glucose in saline or distilled water for diabetic coma, blood, sera, vaccines, and arsenicals; the contraindications being adhesions, peritonitis and marked distention. Glucose aggravates an existing enteritis. It cannot be overlooked, however, that reactions occasionally occur—elevation of temperature, distention, aseptic peritoneal irritation, and even collapse and death—and while the intraperitoneal method is undoubtedly excellent for saline or Ringer's solution, it should not be used indiscriminately or without careful estimation of all factors involved.

Roentgenography of organs and parts hitherto not demonstrable by this method of study is now becoming possible through the medium of thorotrast,[19, 20] a 25 per cent colloidal solution of thorium dioxide. This is a substance of high dispersion which becomes fixed in the cells of the reticuloendothelial system, and is of such low toxicity that the lethal dose has not yet been determined. It is introduced intravenously in divided amounts on several successive days. After allowing three or four days for the particles to become fixed, the main divisions of the reticuloendothelial system are easily shown. The material remains in the cells for many months without apparent effect as there have been no unfavorable reactions in many experimental animals or in patients. The parts visualized include the liver, spleen, brain, genitourinary system, blood vessels of the extremities, fistulous bronchial tracts and empyema. It should prove of value in differential diagnosis of tumors, as an aid to encephalography, in conditions of the kidney when other methods of urography are unsatisfactory, and no doubt in other conditions as its use becomes more popular.

Peroral endoscopy for the discovery and removal of foreign bodies in the respiratory and upper alimentary tracts[21] is a most valuable and often a life-saving procedure, but on account of the technic and the instruments required, it is still distinctly in the domain of the spe-

cialist. When the history does not indicate a foreign body, the symptoms may be confusing. The following are suggestive—initial coughing, choking or gagging, regurgitation or difficulty in swallowing, respiratory difficulty immediately following an operation on the upper respiratory tract, asthmoid wheeze (suddenly acquired asthma is very rare), a slap or thud upon auscultation, or an atypical pneumonia. Radio-opaque substances occasion little difficulty in diagnosis, but many bodies cannot be thus seen. Vegetable substances in the bronchi produce inflammatory reactions, a partial block causing obstructive emphysema and a complete block, obstructive atalectasis. Bronchi full of secretion may be mistaken for pneumonia and continued bronchial irritation may result in abscess, fibrosis or bronchiectasis. In the cases of lung abscess the possibility of a foreign body is always to be considered. If lodged in the esophagus a foreign body may perforate, causing mediastinitis or hemorrhage. When lodged in the respiratory tract or esophagus it should always be removed, but when in the stomach or intestine it may be watched daily by means of the x-ray and operation considered only if progress stops. Most foreign bodies which enter the stomach can also pass, the exceptions being objects which on account of inability to make the turns in the duodenum should be removed. Catharties are contraindicated. Most objects will pass without assistance but oftentimes directions to eat foods containing fiber or other indigestible residue, agar or even to swallow a bolus of chewing gum and report the results in 24 to 48 hours, have an excellent effect upon the alarmed parents and do no harm to the child.

Laryngeal stridor in infants, while usually due to thymic pressure, may be caused by the infantile type of larynx.[22] Direct inspection of the larynx is indicated always and x-ray treatments will give relief when the stridor is due to thymic enlargement. Intubation is apt to damage the infantile type of larynx. If the stridor is severe, tracheotomy is indicated and after two or three months the normal growth of the larynx will relieve the condition. Tracheotomy in the newborn seems a rather radical procedure, and unless the stenosis is sufficient to cause exhaustion or make suffocation seem imminent, it would seem logical to reduce activity and follow a more conservative course while waiting for normal growth to effect the cure.

The problem of increasing the length of a bone following poliomyelitis, fracture or congenital defect has long taxed the ingenuity and resources of the orthopedic surgeon. Mechanical stimulation of the epiphyseal line, radiation, stimulation of general metabolism, plastic lengthening of the bone, and shortening of the opposite limb, have all been tried with varying degrees of success or failure. For this reason an observation by Ferguson[23] deserves careful consideration. He finds that before union of the epiphyses has taken place the longitudinal growth of the metaphysis may be stimulated by interruption of the medullary blood supply while leaving the periosteal supply intact. A hole is drilled through the cortex midway between the middle of the bone and the epiphyseal line and the medulla thoroughly interrupted with a curet. No premature union of the epiphysis occurs and he reports a gain of one-eighth inch annually for each epiphysis or about 30 per cent increase over the normal gain of the corresponding bone of the opposite side. One can only speculate upon the cause of this in-

creased rate of growth but it would seem probable that it is due to the development of a hyperemia or an increased circulation to the epiphyseal region and perhaps is comparable to the increased rate of growth at times noted after a fracture. If this increase can be controlled, the procedure may open a new field in the correction of postpoliomyelitic deformities.

Instances are still too frequently encountered in which the correction of congenital clubfoot is delayed until the infant is six to twelve months of age. Treatment should be begun on the day of birth, thus taking full advantage of the most plastic period of development. Every day of delay increases the difficulty of correction and diminishes the possibility of a perfect result. Royle[24] uses a molded plaster splint in cases of talipes equinovarus, correcting the varus by gentle, steady pressure and changing the splint every two or three days as correction progresses. Three weeks is usually sufficient to obtain a good correction. The equinus is then treated by placing a shaped board on the sole and inducing a progressive dorsiflexion by traction upward toward the knee with adhesive plaster. This is changed frequently and when good overcorrection has been obtained a shoe with a firm sole may be fitted. A strap passes from the outer side of the sole upward to a laced leg cuff maintaining the overcorrected position during the period of rapid growth. The correction is quite rapid and should not cease until the dorsum of the foot approaches the anterior surface of the leg. The corrective shoe should be worn until the child walks with no sign of deformity. Other forms of congenital talipes are treated by adaptions of the same method. It is our experience that parents are prone to become careless, with resultant relapses, and hence it is advisable to insist that the child be kept under observation for not less than five years, reporting at stated intervals for inspection.

In the treatment of cutaneous burns nothing has been developed which equals the immediate tannic acid treatment. After the removal of débris and raised skin a spray of recently prepared 5 per cent tannic acid is used every fifteen minutes until a brown tanned surface results. Davidson[25] presents interesting statistics showing that 45 per cent of lethal burns in the United States are in children under the age of six years; that up to three years more boys than girls die; that at nine years twice as many girls as boys die, the reason probably being the difference in clothing; that a burn of one-seventh of the body surface may be fatal in a child as compared to one-third in an adult; and that the immediate mortality is influenced by the extent of the burn while the ultimate mortality depends upon the depth. Complications are rather frequent and serious. Skin grafting which is a valuable measure in preventing contractures must frequently be delayed because the condition of the child does not permit the administration of a general anesthetic, and many children are psychologically unsuited for the use of local anesthesia. There is always concentration of the blood to a greater or less degree, often requiring the intravenous administration of fluid. Saline should be used instead of glucose solution as the blood shows a low chloride and high sugar content. Blood transfusion is of value in raising resistance and supplying easily assimilated food. Scars and contractures develop from heaped-up granulations, so these should be kept down, and covered with skin grafts as soon as the general condition will permit.

Few conditions met with in infants and children are as distressing as these burns. They tax the patience, time and resources of the attending physician to the utmost. Davidson's contributions to the subject have resulted in the saving of many lives.

Plastic surgery in infancy and childhood is applicable to a great variety of conditions. In a recent review New[26] points out the importance of careful preoperative planning, careful and exact technic, and careful postoperative treatment as necessary factors in obtaining good results. Failure in any one of these respects may nullify the most painstaking efforts in the others. Thiersch and full thickness grafts either free or over a form, lined grafts, pedicle and tubed grafts, and the plastic swinging of flaps all have distinct fields of application. The incorporation of foreign substances is of questionable value, cartilage giving much better support and greater permanence of structure. Among the conditions to which this type of surgery is particularly adapted may be mentioned contractures and scars from burns, distortions due to trauma, and the many congenital defects such as malformations of the ears and nose, epicanthus and ptosis of the lids,[27] cleft lip and palate,[28, 29, 30, 31] malformations of the extremities, hypospadias[32] and other defects of the external genitalia.

Multiple stages are necessary in much of this work and the desire to progress too rapidly often leads to loss of essential tissue and ultimate poor results. When treating these conditions in young children and infants the ability to estimate future growth and to take full advantage of physiologic reactions is fully as important as accurate technic. The power of muscular pressure will narrow a cleft in the palate and close an alveolar gap much better than forcible manipulation or the pressure of wires and plates and the result will be better function and more normal appearance. The careful preservation of blood and nerve supply and of muscle attachments permits physiologic function and normal development, whereas the desire to save a few minutes, the failure to work out a definite plan based upon accurate knowledge of anatomy, or the lack of delicacy in handling tissues, while at times giving good healing, will usually produce a functionless structure which may be worse than the original condition. There is much variance of opinion as to the optimum time for operation upon clefts of the lip and palate, each surgeon choosing the time which gives the best final results under his individual technic. It would seem more logical to determine the time for operation upon a physical or physiologic basis than upon a chronologic one, and to operate when the general nutrition, weight and blood picture have approximated a certain standard rather than when the infant has completed a certain number of days of extrauterine existence.

A detailed review of plastic surgery is impossible because of the infinite variety of conditions which require individual treatment and the necessity of ingenuity in meeting them. Much of it appears simple and easy, and it is often considered of minor importance by the surgeon whose time is devoted largely to the excision surgery of adults. No greater mistake can be made than to approach a problem of plastic surgery affecting the face of a child in this spirit, for the results of failure are constantly in evidence and may become, for the individual concerned, worse than death—a handicap which even a brilliant mind or signal ability in later life is unable to overcome.

The statement is frequently made that x-rays of the thymus are particularly necessary before surgical procedures upon infants with congenital defects. In regard to this we are in complete accord with Talbot[33] that most of our ideas upon the subject of thymic death are "unsubstantiated and without scientific proof."

Appendicitis continues to be responsible for a greater amount of medical literature than any other condition, over 1700 articles having appeared in the past three or four years, and a steadily increasing proportion of these deals with appendicitis in children. Many writers refer to the gradual but continuous increase in mortality[34] and several claim that this is an unenviable distinction of American surgery. Whatever a careful analysis may show, it is unquestionable that the mortality in children is unnecessarily high and that it is increasing. Graham[35] states that for children there has been 8 per cent increase for the entire United States in the past five years with this figure rising above 50 per cent in the statistics of the individual states. In a discussion before the Royal Society of Medicine[36] it was stated that the operative mortality of this condition in England has been reduced greatly by the general tendency to operate early in the course of the disease, although there was considerable variance of opinion as to the optimum time for surgical intervention.

In the search for causes of the high mortality in children all conceivable angles have been explored, even the economic depression coming in for its share of the blame. The association with inflammatory conditions in other parts of the body is noted, particularly the tendency to follow infections of the upper respiratory tract, which are so common in children. Six cases have been reported[37] of association with mumps, the question of metastasis comparable to orchitis being raised. Graham mentions the psychology of childhood with the inability or disinclination of some children to admit pain or tenderness and their lack of cooperation with strangers. The rapid course of the disease with early perforation he considers due to the delicacy of the tissues and mentions the frequent incidence of peritonitis, stating that 95 per cent of all peritonitis in children is due to appendicitis. Early diagnosis is particularly important and requires an estimation of all factors —history, physical examination, course and laboratory aids. Differentiation from intrathoracic conditions is at times most difficult, three cases of pericarditis being reported[3] in which normal appendices were found at operation. In these cases postoperative review brought out the facts that there was a history of rheumatism in two and of mitral insufficiency in the third, that one had arthritis, that symptoms of general systemic infection were pronounced before the onset of abdominal symptoms, that there was no definite localization of tenderness, and that all three patients complained of pain in the neck. Age is apparently not an etiologic factor. The disease occurs in infants as well as children and has even been reported as an intrauterine infection with death on the third day.[35]

The surgical care of a case even after the diagnosis is made is a most controversial subject. Operation on first sight, conservative treatment, removal as soon as the diagnosis is made, delay in subsiding cases, obligatory removal, incision or absorption of localized abscess, risk in the presence of spreading peritonitis, to drain or not to drain, remove one type but leave another, no operation during the period

of the third to seventh day, are all points which have their enthusiastic advocates or vigorous opponents. Study of the innumerable conflicting opinions coupled with reasonably extensive experience inevitably results in the conclusion that in the last analysis it is a question of surgical judgment and "judgment has always been accounted the most difficult part of our art."[36] Adherence to an inflexible rule is a fertile source of mortality and may be taken as an admission of lack of judgment. In no condition is it more important to abandon adult comparisons and rely upon the principles of surgical pediatrics. Diagnosis requires appraisal of the statements of both patient and parents, of the significance of posture and respiration, of reaction to environment and stimuli, and a pediatric approach in physical examination and interpretation of laboratory findings. It is easy to elicit general abdominal rigidity with a cold hand or too vigorous palpation. A normal leucocyte count may be a danger signal, and a high one a welcome reassurance. The determination of optimum time for operation involves estimation of the state of nutrition and hydration, of the reaction of the body to the infection, and of the course of the pathologic process. Surgical intervention too often becomes surgical interference or even surgical assault if undertaken during the stage of falling or low resistance rather than when antibodies have developed, or before reactive ability is lost. In the conduct of the surgical procedure judgment again is vitally essential, and delicacy of manipulation, respect for defensive mechanism, and ability to estimate and take advantage of physiologic reactions are paramount.

No fixed rules can be laid down for the reduction of the mortality of appendicitis in children. The factors are as diverse and intangible as economic stress, medical curricula, the personal equation of patient, parent, and doctor, professional ethics, operative facilities, types of infection, body resistance, technic, preoperative and postoperative care; but greatest and all-inclusive is the factor of surgical judgment.

In an analysis of 42 cases of acute peritonitis Lazarus[39] finds a mortality rate of 70 per cent for the pneumococcic type, 85 per cent for the nonpneumococcic type, and 30 per cent for the type secondary to appendicitis. Contrary to the usual teaching the pneumococcic type is not due to extension through the tubes, is not more common in female infants and children, and does not follow pneumonia, but is usually secondary to an upper respiratory tract infection. Early diagnosis in infants is unusual and rather difficult, being best made by aspiration and examination of the peritoneal fluid. Laparotomy and drainage within three days of the onset offers the best hope of recovery. Disturbing therapeutic measures are bad and transfusions of no value. Prognosis is generally poor. In peritonitis of appendicular origin serotherapy[40] is receiving some attention. Its value is not yet definitely established but Prochnow's report is encouraging.

Mesenteric tumors both cystic and solid are described by Rankin and Major[41] without mention as to their occurrence in children. Malignant tumors have usually extended by metastasis before the diagnosis is made and hence are not favorable for surgery. Cystic tumors, however, are usually benign and the surgical prognosis is good. Both dermoid[42] and chylous[43] cysts have been reported. Two instances of chylous mesenteric cysts have occurred in the surgical practice of the reviewer, one causing intestinal obstruction and the other marked abdominal distention without acute symptoms.

Mesenteric thrombosis while fortunately infrequent is a condition which is always serious and usually fatal. An excellent experimental study[44] has demonstrated the possibility of successful surgical treatment if the diagnosis can be made early, with the exception of those cases involving an extensive venous block. The effects of mesenteric thrombosis or embolism are similar to those of acute intestinal obstruction but if surgery is delayed until distention and vomiting occur, such extensive damage has already taken place that all treatment is hopeless. Roentgenograms in the upright position will show gas and fluid levels several hours before definite physical signs and symptoms develop. By a similar study of intestinal obstruction the same authors[45] have demonstrated gas and fluid levels within four hours after the obstruction has been produced. Comparison with clinical cases of the distention frequently seen in infants and small children shows that the distended loops of bowel do not show fluid levels and the distention of individual loops is transient, whereas in cases of obstruction fluid and gas levels are present and location is constant. Soon after obstruction occurs stagnation and decomposition of intestinal contents begins, the power of absorption of the bowel wall above the obstruction is reduced and secretion is increased, quickly producing the gas and fluid levels so well demonstrated by x-ray in the upright position.

The generally accepted clinical signs of obstruction are too frequently late antemortem signs and the diagnosis should be made before they occur. Roentgenologic study at the earliest indication of obstruction will permit surgical relief before irreparable damage has occurred. Opaque meals are unnecessary and may be dangerous because of the delay or the increased intestinal content and are often impossible because of vomiting. Preoperative administration of saline[46] is often valuable to replace fluid withdrawn from the tissues into the bowel. Visible peristalsis is a late sign. A history of sudden onset with intermittent cramps and pain accompanied by loud intestinal borborygmus and perhaps some localized tenderness is sufficient for a tentative diagnosis and a request for x-ray examination. When no mass is palpable and there is not marked tenderness the obstruction is usually due to volvulus, intraabdominal hernia, bands or adhesions.

Intussusception accounts for the great majority of intestinal obstructions during infancy,[47] 50 per cent occurring between the fifth and ninth month and 80 per cent under two years. In older children[48] the condition is more frequently subacute and recurrent and may simulate appendicitis or tuberculous peritonitis. An afebrile appendicular syndrome in the right upper quadrant is very suggestive. In infants, however, the diagnosis is usually not particularly difficult, sudden intermittent abdominal pain in a previously healthy, strong infant, no fever, facial appearance of peritoneal shock during the attacks of pain with normal color and expression between, bowel movements showing an increasing amount of mucus changing to the currant-jelly type in the later stages, vomiting and distention also as late developments, palpation of a smooth, moveable, sausage-shaped tumor during the intervals between cramps or the end of the mass by rectal examination, all give a characteristic picture. Mechanical methods of reduction are at times successful in the earlier cases but later are dangerous because of the possibility of rupture of a devitalized bowel.

Water under pressure of 2-3 feet, air under moderate pressure and barium under 3-4-foot pressure with gentle manipulation under the fluoroscope have been recommended,[47] but the results are so uncertain that laparotomy is usually advisable to be sure that reduction is complete. Reduction within 24 hours of onset is usually easy with nearly 100 per cent recovery, and many series of cases show no deaths when reduction is effected within 36 hours. After this period, however, the mortality rate rises with extreme rapidity until the percentage of recoveries after three days is extremely small.

Gentleness in handling the bowel, a minimum of manipulation, conservation of body heat, and accessibility of the tumor mass are essential for success. One article has appeared in which the author recommends traction upon the uninvolved bowel at each end of the mass to effect reduction. Such a procedure cannot be too strongly condemned because of the grave danger of tearing the edematous bowel wall. Reduction should be accomplished by gentle, firm pressure from the distal end which tends to reduce edema and gradually forces the involved portion of bowel out in a retrograde direction. When the intussusception is irreducible, immediate resection gives an extremely high mortality rate, a series in which the rate following resection was only 76 per cent[49] being by far the best which has come to our attention. When reduction cannot be accomplished, it is best to exteriorize the mass and do an enterostomy or short circuit operation, resecting later if necessary. Fixation to prevent recurrence although frequently advised is, in our opinion, of doubtful value. The bowel wall at the end of the intussusception is usually so markedly thickened by edema that recurrence for some time would appear impossible and the complete disappearance of dense inflammatory adhesions which is so often observed in children would make the permanence of induced adhesions seem extremely doubtful. The strong tendency of reparative physiologic processes to restore normal anatomic conditions is rendered most effective by the active metabolism of the developing period.

Meckel's diverticulum[50] may cause intussusception, or obstruction due to volvulus, or a loop of intestine may become strangulated by a congenital band or an inflammatory adhesion between the diverticulum and the abdominal wall. Inflammation of a Meckel's diverticulum[51] presents a difficult diagnostic problem as it may simulate any of the more usual acute abdominal conditions and its presence should always be suspected if a normal appendix is found following symptoms of acute appendicitis. It is interesting to note that gastric mucosa has been found in these diverticula[52] and ulcers may occur giving rise to acute or chronic symptoms simulating ulcer higher in the alimentary tract or tuberculous enteritis or peritonitis. Occult or upper intestinal blood in the stool may come from such an ulcer and its presence during the course of obscure abdominal complaints may lead to a correct diagnosis.

In all types of obstructive distention intestinal decompression is a most valuable therapeutic measure.[53] It may be used to advantage before operation in cases of strangulation and may even render operation unnecessary in cases of simple obstruction. Suction siphonage is induced by passing a duodenal catheter through the nose and connecting it to a system of bottles, the strength of suction being governed by the siphon principle. The tube may remain in place several days if necessary.

Visualization of the fluid spaces of the central nervous system has become a diagnostic measure of proved value,[54] not only in the localization of tumors but also in epilepsy and traumatic or inflammatory meningeal conditions. In cases of physical or mental abnormality with a demonstrable brain defect it is often a priceless boon to parents, for by this means the diagnosis can be demonstrated to the lay mind with a finality which puts an end to anxious and futile professional wanderings and will-o'-the-wisp excursions after cults. A definite certainty, no matter how bad, is preferable to an uncertainty.

Among clinicians there is still much skepticism as to the accuracy of interpretation of encephalograms but careful study[55] by means of wax injections and autopsy findings has reduced error and made it possible to read encephalograms in terms of anatomy and pathologic processes with a high degree of accuracy. This ability, however, is attained only by experience and an intimate familiarity with the conditions studied, and nowhere have we yet found a treatise in which the information is sufficiently detailed and comprehensive to enable the average roentgenologist or clinician to be certain of making even approximately correct interpretations. The use of thorotrast as noted earlier in this review may be of aid in encephalography by increasing the accuracy of diagnosis of various tumors and vascular anomalies of the brain, but as yet no reports of this use have appeared.

Cisternal puncture for diagnostic or therapeutic purposes is a procedure of recognized value. It is usually simple and comparatively easily performed upon children. It should not be used, however, in the presence of indications of intracranial tumor and at all times should be performed carefully, as medullary injury[56] and sudden death have been reported.

The various forms of vascular birthmarks are well described by Kromayer.[57] Arterial nevi are red, raised and moderately compressible. They may be so small that they are not noticed at birth but soon begin to grow, reaching a diameter of one or two centimeters. A period of rapid growth may follow incomplete destruction by heat, cold or caustics. They are best treated by radium. Capillary nevi are usually smooth and flat although occasionally slightly raised. They may be very extensive, involving the lower layers of the skin down to the subcutaneous tissues and varying from light red to a dark blue color. A single thorough treatment with water-cooled ultraviolet light (Kromayer lamp) will frequently remove them. If such a treatment is not effective it should not be repeated, but radium or x-ray used instead. These are rather intractable and may be only improved rather than cured under any form of treatment. These are not to be confused with the so-called "port-wine marks" which our observation indicates do not respond to any form of treatment, and parents should be warned that attempts at removal may easily result in greater disfigurement. The large venous nevi consist of greatly dilated capillaries derived from the deeper layers of the skin or from the subcutaneous tissues. Lying in loose connective tissue they become elevated, sometimes to a very marked degree, are soft and compressible and bleed easily. The small and medium-sized ones may be easily excised or treated with radium or x-ray, but for the large deep-seated ones x-ray or radium is preferable to surgery. When they occur on the extremities these may become cavernous following trauma,[58] even enlarging to the extent of causing apparent hypertrophy of the limb.

The necessity of treating this type of birthmark during childhood is evident when it is realized that the enlargement may become so disabling as to require amputation in later life.

True hemorrhagic purpura responds well to splenectomy,[59, 60] but the indications must be exact and definite as the mortality rate in atypical cases is high. Requirements are (1) recurrent hemorrhages under the skin or mucous membranes, (2) definite enlargement of the spleen, (3) low platelet count, (4) prolonged bleeding time, (5) normal coagulation time, (6) non-retractile clot, (7) no marked variation in the erythrocytes or leucocytes except at times the usual changes due to secondary anemia, (8) a positive tourniquet test—showers of petechiae immediately following the application of a tourniquet. These requirements are obligatory and any variation from them throws the case into the atypical class. The etiology is obscure. Toxemia has been suggested as a possibility and the removal of all demonstrable foci after splenectomy is advised to prevent recurrence. The gradual recurrence of the blood picture in some cases without clinical symptoms or hemorrhage suggests that the diminution in platelets may be secondary to the true etiologic factor and that clinical recovery following splenectomy is concomitant with, and not consequent upon their restoration. The relief of clinical symptoms is often spectacular, hemorrhage frequently ceasing before the abdomen is closed and normal bleeding time returning almost immediately. The return of the platelets is slower—from one to two weeks—but there is a sudden marked increase in leucocytes, the count remaining high for as long a period as a year. The prognosis is good, a mortality of 7.08 per cent being reported in one series of 113 carefully worked out cases[60] with the chronic type slightly more favorable than the acute. In few conditions is absolute adherence to definite diagnostic points so important. Preparation by means of transfusion, rest and care, before depletion from repeated hemorrhages has occurred and the employment of a high type of surgical skill are essential to success.

An interesting blood dyscrasia in which splenectomy seems to offer hope is erythroblastosis of the newborn.[61] This condition is characterized by a rapidly developing jaundice within a few hours after birth with marked hemolysis, great numbers of nucleated red cells and a high icterus index. The jaundice is in reality a pesudojaundice as there is no deposit of pigment in the skin, the color being due to the color of the plasma in the capillary bed. Transfusion is excellent at times but in some instances has served only to increase the blood destruction and death has occurred within a short time. Recovery has followed splenectomy which is always advisable if improvement is not immediate upon transfusion. It is increasingly evident that splenectomy has more far-reaching and complex effects than are explainable at present by the information at our disposal.

A symptom appearing in the course of blood dyscrasias of the leucemic type may be respiratory distress,[62] suggestive of thymic obstruction and occasionally, in these cases, the roentgenogram shows a rather dense, sharply outlined mediastinal shadow. This is not considered to be a true tumor but rather a cellular infiltration which disappears under x-ray treatments. A peculiarity of the condition is that the treatments give relief only if instituted before development of the typical blood picture of the disease, treatments subsequent to the de-

velopment of this picture only aggravating the condition. Whatever relief is obtained is purely symptomatic and does not alter the prognosis.

Favorable reports of the treatment of Hirschsprüng's disease by sympathectomy are continuing to appear with indications for the operation gradually crystallizing.[63] Sympathectomy would seem particularly appropriate in the treatment of this condition which is probably of neurogenic origin as it is true physiologic surgery and finds its greatest application in the treatment of dysfunction of vessels, smooth muscle and glands. The sympathetic nerve supply of the sigmoid and affected portion of the colon is interrupted either by section of the rami or by excision of a portion of the sympathetic trunk, in which connection it is particularly important to go above the level of the first lumbar ganglion.[64] Section of the presacral and inferior mesenteric nerves is also recommended. Symptomatic recovery is the rule, although the establishment of an anatomically normal colon is slow and even may fail to occur. Treatment by colostomy or colectomy is usually unsatisfactory and has a deterrent mortality although in cases of marked redundancy of the sigmoid and of dolichocolon good results have followed excision with end to end anastomosis.[65]

Congenital hypertrophic pyloric stenosis together with other congenital anomalies of the alimentary tract have been excellently summarized by Bonar[66] in the Critical Review of the Newborn, to which the interested reader is referred.

Peptic[67] and duodenal ulceration[68] in infants and children occur with sufficient frequency to merit careful consideration in the study of intractable digestive disturbances, over 200 cases having been reported, the great majority occurring under the age of five months. The cause has not been determined. The history in cases of peptic ulcer is that of a chronic digestive disturbance without apparent cause, with the finding of occult blood in the stool and roentgenographic demonstration of gastric deformity. In cases of perforation surgery is, of course, indicated, but the mortality is high and perforation rarely occurs if medical treatment is instituted early and pursued consistently. Vitamin C deficiency should be avoided and foci of infection eliminated. Vomiting with consequent failure to gain, pain after food, blood in the vomitus or diarrhea in about 50 per cent of the cases, and marasmus of obscure origin in an infant under five months of age is a syndrome warranting a tentative diagnosis of duodenal ulcer, but a definite diagnosis is rarely made before autopsy. The prognosis is poor under any form of treatment.

The frequent failure of vesical dysfunction to respond to the usual forms of therapy—physical, medicinal and psychic—is evidenced by an increasing interest in a possible neurogenic etiologic factor.[69] Any condition which alters the normal nerve impulses to the bladder may result in some degree of retention or incontinence. The possibility of such alteration being caused by an osseous defect of the lower spine[70, 71] or by defective neuromuscular mechanism[72] is always to be considered and search for spina bifida occulta is indicated in all functional defects of obscure origin. Abnormal nerve impulses may be due to the impingement upon nerve roots of scars or fibrous deposits resulting from inflammatory conditions of the meninges, and release of the nerves may result in restoration of normal function. The correction of urinary retention by sympathectomy has been successful in some cases but

the possibility of disturbance of nerve balance is difficult to calculate and a late sequel may be incontinence. Plastic reconstruction of the vesical sphincter requires a high degree of skill, optimism and perseverance and has not yet reached the stage of perfection which gives assurance of even a fair percentage of success.

Location of the causative factor of urinary disorders[32] often taxes our diagnostic resources to the utmost, cystoscopy, cystography, intravenous urography,[73] neurologic study and roentgenography of the spine being used as necessity indicates. With the development of small instruments study of the urinary system is as readily accomplished in infants and small children of both sexes as in the adult, and many persistent pyurias respond with gratifying rapidity to appropriate surgical treatment of mechanical obstructions revealed by such study. Dilation of the entire tract may be due to a small meatus and be readily treated by free meatotomy. This is also the treatment indicated in painful micturition following urethritis with crusting, if the meatus is narrow. Dilation above the urethra may be due to congenital narrowing of some portion of the tract, to pressure of aberrant or anomalous blood vessels, to valve-like folds of mucous membrane or to stricture of the ureteral orifice. The presence of such dilation predisposes to the development of intractable pyuria following acute infections which may go on to renal destruction or perinephritic abscess.[32] In addition to the usual symptoms and signs of infection, perinephritic abscess usually gives tenderness and fullness in the flank or lumbar region and the x-ray may show obliteration of the outer border of the psoas muscle with flexion of the spine toward the affected side. Incision and drainage is usually followed by prompt recovery. In extensive unilateral renal infection, nephrectomy is indicated when thorough persistent treatment has failed to produce results and careful study has demonstrated the competency of the opposite kidney. Renal lithiasis may be treated by dietary regulation if the stones are small but surgical removal is necessary for the large type which fill the renal pelvis. Vesical calculi may be crushed, but removal by the suprapubic route is usually not difficult and insures thoroughness.

Renal tuberculosis[74] is rather frequently encountered in tuberculous children under ten years of age, marked destruction of the kidney being commonly seen because of late diagnosis. Bilateral cases develop distressing vesical symptoms and are rapidly fatal. Nephrectomy in unilateral cases is fairly satisfactory and offers good hope of recovery if the lungs are sound. The operation should be preceded by a regimen of rest and diet with preoperative blood transfusion and should be followed by prolonged sanatorium treatment. Careful urologic study is usually necessary for diagnosis, intravenous urography being valuable. Retrograde pyelography is condemned as unreliable and dangerous.

The kidney is the site of 20 per cent to 25 per cent of all malignancies occurring during the first decade of life. Mixter[75] considers the terminology of sarcoma and carcinoma incorrect, preferring to designate the mixed cell type as embryoma and that derived from the adrenal medulla as neuroblastoma. These tumors usually develop before the age of five years and have been found repeatedly in the fetus, embryoma occurring with three times the frequency of neuroblastoma.

The course of the disease is silent, subjective symptoms being lacking and the first evidence of abnormality being an increase in the size of the abdomen or the discovery of a mass. Secondary anemia, emaciation and dilation of the abdominal veins are late signs. The child may be irritable and uncomfortable but even in the terminal stages the course is usually mercifully painless. Diagnosis presents few difficulties. The author considers urography and cystoscopy unnecessary in most cases, but with the safety and simplicity of intravenous urography and the use of thorotrast it would seem advisable to determine the presence of a horse-shoe kidney or other anomaly which might prove disturbing if encountered unexpectedly in the course of the operation. Removal should always be attempted regardless of the size of the tumor except in the presence of definite metastases, which occur in the liver, chest and skull. Important factors in successful treatment are good preoperative and postoperative care, transfusions, hemostasis, gentleness in handling tissue, careful conservation of body heat and early operation—before the age of twelve months. The transperitoneal route is the best, particularly in the larger tumors. Between three and six months after operation recurrences are apt to appear, pursuing a rapid course to fatal termination in less than a year.

The treatment of hypospadias[32] presents difficulties which merit the most careful preoperative study and planning and the most exact operative technic. Preliminary suprapubic cystotomy with continuous drainage is usually advisable regardless of the apparent simplicity of the condition. Whenever possible the repair should be completed before school age to avoid the inevitable observation and remarks of schoolmates with the resultant unfortunate psychologic effect. Winsbury-White[32] describes an operation for the repair of the penile type of hypospadias in which the prepuce is transplanted to the anterior surface of the scrotum with the mucous surface upward. The penis is next turned downward and attached, using this surface to form one side of the urethra and finally the preputial transplant is separated from the scrotum and the raw surfaces covered by plastic sliding flaps.

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American Academy of Pediatrics

Proceedings

THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

TUESDAY AFTERNOON
June 13, 1933

Business Session

The meeting was called to order at 2 P.M. by the Chairman, Dr. Samuel McC. Hamill.

President Hamill read his address. (To appear in full in the September number of the Journal.)

President Hamill.—The next order of business is the report of the Executive Board which will be made by Dr. John Ruhräh.

Dr. Ruhräh.—The Executive Board has held two meetings during the year, one in November in Chicago and the other one this morning. The greater portion of the business transacted by the Board this morning will be presented in the report of the Secretary-Treasurer.

Dr. Ruhräh presented the report of the Executive Board. (November meeting was published in the Journal in January, 1933, p. 118.)

President Hamill.—You have heard the report of the Executive Board. What is your wish in regard to it? There are certain amendments to the by-laws proposed. These have been properly circularized in order to comply with the requirements relating to the amendments to be acted upon at this meeting.

Secretary Grulee.—The principal amendment is that to Section 6 of Article IV.

Secretary Grulee read Article IV as at present printed and the proposed amendment.

President Hamill.—You have heard the proposed amendment to the By-Laws, what is your wish in this respect?

Dr. Thomas B. Cooley.—I move the proposed amendments be adopted.

The motion was seconded and carried.

Secretary-Treasurer Grulee then presented his report; also the minutes of the Executive Board meeting held June 13, 1933.

Report of the Executive Board

A meeting of the Board held at Edgewater Beach Hotel, Chicago, Tuesday morning, June 13, 1933, was called to order at 11 A.M. by the President of the Academy Dr. Samuel McClintock Hamill. The following were present:

Doctors Samuel McC. Hamill
John Ruhräh
Charles A. Aldrich
Edward C. Mitchell
Jay I. Durand
Frederick F. Tisdall
Clifford G. Grulee

A report entitled "Standard Measures for the Prevention of Communicable Diseases" presented by Dr. E. B. Shaw, San Francisco, California, was submitted to the Board. It was voted that this matter be referred back to Dr. Shaw with power to organize a committee as he sees fit and submit said report to the Regional Chairman to determine local needs. A report of such findings to be made at next annual meeting of the Academy.

The Secretary presented a communication from Dr. Edgar P. Copeland, Washington, D. C., relative to adoption of more definite measures of qualification for eligibility to the Fellowship of the Academy. The Secretary was authorized to write a letter to all members that in the future recommendations for new members be sent directly to the Regional Chairman and not to accompany the application.

It was voted that the item of expense of ten dollars, incurred by the special committee delegated to Milwaukee to attend the meeting of the Committee on Medical Education, be approved.

It was voted that a total of ten dollars be allowed the Committee on Hospitals and Dispensaries for expense incurred in connection with the present meeting of the Academy.

It was voted that for each of the members, each state be allocated two dollars for expenses of state committee meetings and that for each of its members, each region be allocated one dollar for office expense of Regional Committees. In addition, that the expense of meetings of Regional Committees be met; such committees to be composed of not more than five members and holding not more than one meeting.

The Secretary presented the auditor's statement for the fiscal year which was approved.

The Secretary presented the budget for the ensuing year which was approved.

It was voted that an exhibit on history be arranged in connection with the next annual meeting of the Academy, the details of which to be arranged by the Secretary, the Academy to pay for the expenses of exhibit, to consist of transportation and booth.

The matter of conducting round table conferences similar to those held in connection with the present meeting was discussed. It was the consensus of opinion that a similar arrangement be made in connection with the next annual meeting.

It was voted that the next meeting of the Academy be held on Monday and Tuesday preceding the meeting of the American Medical Association, that if the meeting of the American Medical Association be held in Atlantic City, the meeting of the American Academy of Pediatrics be held in Philadelphia or vicinity; if the meeting of the American Medical Association be held in a city other than Atlantic City, arrangements similar to those of the present year be made by the Secretary.

It was voted that Dr. Borden S. Veeder be appointed to represent the Academy as a member of the Examining Board for certifying candidates.

It was voted that Dr. S. McC. Hamill be appointed to represent the Academy in the Children's Bureau.

It was voted that Dr. W. E. Blatz of Toronto and Dr. E. Gorter of Leiden, Holland, be made associate members of the American Academy of Pediatrics.

Report of Secretary

There are, at present, in the Society 538 active members and 11 associate members. During the past year, we have lost one member, Dr. Orville R. Chadwell of Boston, through death, and Dr. Rowland G. Freeman and Dr. Robert G. Sharp through resignation.

The Secretary has made three extensive trips during the year. One to Indianapolis, Indiana, where he met with the Indiana group. One to Birmingham, Alabama, for the meeting of Region II during the Southern Medical Association meeting, at which time they organized the plans which will be reported by the chairman of that region. The Secretary also took a tour through the East stopping at New York and Boston to look into the situations there. He also went to Peoria, Illinois, for organization of work in his own state.

The Executive Board has held two sessions, one on November twenty-sixth and twenty-seventh, the other this Tuesday morning, June thirteenth, report of which you have already received.

In the various regions, Region I has had no general meeting; Region II has had a meeting already referred to at the time of the meeting of the Southern Medical Society in Birmingham; Region III will hold its annual meeting in connection with the Central States Pediatric Society in September. Region IV had a clinical meeting in San Francisco the latter part of October. Region V is not yet developed.

Efforts have been turned toward developing state organization and these we may readily say have been quite successful. The various regional chairmen will give you a detailed account of these activities, but they bid fair to take up a large part of our effort in the future.

Of the special committees, that on Medical Education has been most active and their report which follows will be most enlightening, I am sure. The Committee on Hospitals and Dispensaries has, too, begun the work on the survey of hospitals which will be reported on later. Of the other committees very little can be said. Some of them involve the expenditure of large sums of money if they are to be successfully carried out. Others, such as Nursing Education in Pediatrics, depend largely upon the activities of other committees such, for instance, as that on Hospitals and Dispensaries.

The lean years have had one salutary effect upon the organization, that is, that they have given the members ample time to engage in activities associated with organization. We have, therefore, had very hearty cooperation from all members when called upon almost without exception and I feel very definitely that the organization is beginning to accomplish its purpose and to have a direct effect upon pediatric problems in this country.

One of the most successful accomplishments of the organization has been the launching of a creditable journal in pediatrics. The credit for this is largely to be placed on the heads of the editors, Dr. Borden S. Veeder and Dr. Hugh McCulloch. The Journal may now be said to be a going concern and to be recognized as an excellent Journal by the pediatricians of the country.

"The county society can best serve the interests of the children of our country and its own members by the appointment of a Child Welfare Committee."

It is gratifying to note that a committee was appointed directly after that, and that a similar letter, directed to the State Society, will meet with a like response is our hope. Thus with a state committee working as one unit and with similar committees in each of the county societies acting as co-units it is hoped to develop statewide plans in which the pediatrist shall play the part his interests and education entitle him to.

A survey of the needs of New York State from a child welfare standpoint it is hoped will be published later; but this much is very apparent now, there is a great deal of work to do.

Treasurer's Report

The finances of the organization are still in good condition despite the hard times and resultant reduction in annual dues.

Rather than take up the various items of receipts and expenditures I have had this mimeographed and placed in your hands for your perusal. The books have been audited by a professional auditor and have been found in order.

Respectfully submitted

Treasurer.

AMERICAN ACADEMY OF PEDIATRICS

Statement of Receipts and Disbursements

For Thirteen Months Ending May 31, 1933

Balance, May 1, 1932		$ 9,892.33
Receipts		
Initiation Fees	$ 3,460.00	
Dues	6,325.00	
Transferred from Savings Account	5,000.00	
Exhibits	625.00	
Interest Government Bonds	150.00	
Interest Bank Account	22.92	
		15,582.92
		$25,475.25
Disbursements		
Salaries		
Secretary	$ 5,200.00	
Stenographer	1,675.00	
Subscriptions to Journal	2,550.00	
Annual Meeting	811.18	
Traveling Expense		
Executive Board	$342.29	
Secretary	154.99	
Region I	234.28	
Region III	365.21	
Region IV	68.25	
Committee on Med. Ed.	141.80	
	1,306.82	
Printing and Stationery	195.62	
Postage	223.28	
Office Supplies		
Mimeograph	190.00	
Mimeograph Supplies	$ 49.53	
Miscellaneous Supplies	26.38	
	75.91	
Miscellaneous Expense		
Office	80.70	
Insurance	62.50	
Refunds	35.00	
Telephone and Telegrams	17.84	
Region II (Stenographic Expense)	60.00	
Region I—Meeting Room	10.00	
Exchange on Checks	9.73	
Tax on Checks	2.50	
Express	.42	
U. S. Government Bonds	10,082.95	
		22,589.45
Balance, May 31, 1933		$ 2,885.80

Total Cash

Balance	$ 2,885.80
U. S. Government Bonds	10,232.95
Savings Account	5,304.51
	$18,423.26

Still Due

Initiation Fees	$ 995.00
Dues	1,240.00

President Hamill.—You have heard the report of the Secretary. What is your wish in regard to the report of the Secretary?

Dr. Ruhräh.—I move it be accepted and placed on file. The motion was seconded and carried.

President Hamill.—I am now going to call on Dr. Veeder, Editor of the Journal, to present his report.

Report on the Editorial Board

Dr. Veeder.—First let me express the thanks of Dr. McCulloch and myself for the cooperation we have had in connection with the Journal. A year ago we undertook this work with a good deal of fear and trembling as to what might be the result of such a venture during these times. It has been more successful than we expected.

There are many things we would like to do with the Journal. We can only do those things with the cooperation of the members. We have not had the cooperation from the state chairmen we had hoped for. We conceived the idea of making each state chairman a correspondent so we would have fresh news presented to us from various states as to the activities of the members. We have had very few communications from these representatives. The editors cannot very well go out and get local information.

We would also like to have a great deal more discussion in regard to the various sociologic and economic problems of pediatrics. Dr. Hamill and I have discussed more than once the possibility of getting certain people outside the field of pediatrics to enter into those discussions. So far that has not progressed very far. The editors do not write the Journal; they are limited as to what is put into the Journal by the contributions received.

We have received criticisms to the effect that our Journal is too "highbrow." We have also had just the opposite criticism that it is too "lowbrow," so we feel after all that we have hit a fairly average medium. All we can say is we ask for your continued support. If it is continued during the coming year as it has been in the past year, I think you will see some improvement in the Journal.

President Hamill.—What is your pleasure in respect to the report of the Editorial Board?

Dr. Ruhräh.—I move it be accepted. The motion was seconded and carried.

President Hamill.—We shall next take up the report of the Regional Committees: Region I is to be reported on by Dr. Louis C. Schroeder of New York.

Report of Region I

Louis C. Schroeder, New York

The present membership of Region I is 181. In four states of Region I; namely, New Jersey, Massachusetts, Pennsylvania and New York, far-reaching plans looking toward the development of the best means for linking the Academy of Pediatrics with the welfare of children have been laid.

During the year, one regional committee meeting was held and also state committee meetings in Pennsylvania, Massachusetts, New Jersey and New York, and a local meeting of the New York City Group.

From what developed in the various state meetings it has become increasingly apparent that problems vary according to localities; that the methods of approach will necessarily be different in the different states and that means looking for the most satisfactory solution of the state problems must be worked out, not by executive or regional committees but by each state committee itself.

The value of state chairmen to the development of a vigorous, forward-looking intelligent program in each state cannot possibly be overestimated. In Pennsylvania the Academy has been well represented in the emergency relief work for children, our President serving as the head of that work. In New Jersey, besides the tremendous impulse given to interesting general practitioners in the value of public health measures for children, there has developed a plan for postgraduate instruction in pediatrics of general practitioners by offering courses in New York and Philadelphia which require only one day's absence a week from their practice for a period of nine weeks at a very nominal charge.

In New York the feeling has been that the most effective work can be done through the county medical societies. At the state meeting it was the general opinion, especially after having had two conferences with the head of the State Health Department for Maternity and Child Welfare, that it was the duty of Academy members to foster among the entire organized profession of the state an attitude that child welfare work was not a matter of any group. To this end the following letter was directed to the Executive Committee of the New York County Medical Society:

"The need for cooperation among the various child health agencies in the county has become particularly apparent since the White House Conference. There is no committee in the County Society to undertake the carrying out of the many valuable suggestions formulated by that conference.

"This lack of a representative medical body to carry out such recommendations is unfortunate; it will inevitably lead to lay bodies securing a firm hold on many public health activities which properly belong to the organized medical profession. This situation is distinctly alarming to those of our membership who are in close touch with the problem of child welfare.

"In addition there is a distinct need for linking together many child welfare agencies, some of which, we believe, are unregulated and lack proper or sufficient medical supervision.

"It is common knowledge that the present system employed with preventive measures such as vaccination and diphtheria immunization leave out of consideration the part the physician should play.

"These problems are merely representative of many others which are in need of thorough study by a committee familiar with them and having in mind the all-important part the profession must play in the vital field of child health.

"The responsibility for the solution of these problems lies squarely at the door of organized medicine. If this duty is shirked we can be absolutely certain that lay health and welfare agencies will assume this responsibility.

Report of Region II

Dr. E. C. Mitchell, Memphis

Dr. Mitchell reported the resignation of Dr. Thomas E. Buckman, State Chairman of Florida, and the appointment of Dr. Luther W. Holloway to take his place. There were no deaths or resignations in that Region. Dr. Morgan Smith, who has just been elected to membership, has been made State Chairman for Arkansas.

Dr. Mitchell then reported upon the meeting in Birmingham on November eighteenth at which there were eighty members present, including the Secretary. The meeting was held in conjunction with the health officers of the various southern states and a cooperative program was adopted. This Region has been very active in developing cooperation with health authorities and joint committees have been appointed to act throughout the entire Region. They are also laying great stress on the training of medical students and the principles and welfare of the child. Three committees have been appointed. (All this has been previously published in the Journal.)

A detailed report of the activities in the various states in his region including Arkansas, Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Virginia and West Virginia was then given. He layed stress on the work being done in Georgia since it was a most comprehensive outline showing an immense amount of work done in that state.

The report for Region II was altogether impressive and showed that not only in the states, but also as a Region, work had progressed most satisfactorily. Dr. Mitchell appended to this a report on the Public Health Education Committee of the Knox County Medical Society of Knoxville, Tennessee, which was a local effort well systematized and being carried out with much energy.

Report of Region III

Dr. C. A. Aldrich of Winnetka, Illinois

Dr. Aldrich stated that "in the last two years the emphasis in this region has gradually been shifted from membership efforts to attempts at consummating some of our ideals."

He then gave an account of the work carried on in the various states in the Region including Colorado, Illinois, Iowa, Kansas, Missouri, Nebraska, Ohio and Wisconsin.

He stated that plans had been made for a joint meeting of the Central States Pediatric Society on September 22 and 23, to be held in Chicago. It was anticipated that this meeting will be an annual event and that at intervals it may be possible to combine with Region II in clinical meetings.

Report of Region IV

Dr. Jay I. Durand of Seattle

I shall make a very brief report because our problems and our effort to meet them are the same as those which have been covered in the reports just given. There are at present 56 members in Region IV. Six have been elected since the meeting a year ago and there are five applications pending. During the year a two-day meeting of the Pacific Coast Pediatricians was held at San Francisco under the auspices of the American Academy of Pediatrics and was attended by about fifty pediatricians. The Academy has furnished medical directors for the White House Conference for California and Washington, and the members of the Academy, I think, are leading the welfare movement in all the states on the Pacific Coast. The San Francisco Academy has been particularly active and they are planning to make the Academy members the organization which will direct and control the child welfare health movement. They have nearly doubled their membership in regard to this movement during the year.

Los Angeles likewise has been active.

I think we have made real progress in supplying medical directors for many health agencies which have heretofore not carried on child health and welfare movements, and who have done this work without proper medical directors.

It is rather a surprise to those who have been interested in the movement to

see how interested the lay organizations are and how readily they are carrying on these movements which have been accepted by the medical director. I think there is a field in which much of the work which has heretofore been duplicated can be eliminated and much more effective work can be done.

Region V.—No Report.

Dr. Veeder presented the report of the Committee on Medical Education as already published in the JOURNAL OF PEDIATRICS (2: 501, 1933).

Dr. Veeder.—I move the adoption of the recommendations made by the Committee on Medical Education.

The motion was seconded and carried.

Report of the Committee on Hospitals and Dispensaries

Secretary Grulee.—The Committee on Hospitals and Dispensaries was faced first with the proposition of how large and extensive a survey would be made. It was decided to confine its efforts to the survey of children's hospitals. That sounded very simple. We received a list of the so-called children's hospitals from the Committee on Hospitals and Dispensaries of the American Medical Association. Much to our amazement there were some 120 such hospitals listed. We decided then it was time to find out whether these hospitals were or were not children's hospitals. After writing to members in each of the communities in which these hospitals were located, we were able to bring the list down to thirty-five children's hospitals located in the United States and Canada.

We sent out a questionnaire, the original of which was prepared by us and was decidedly altered by Dr. Van Ingen. We then took these questionnaires and got one member of the Academy to be responsible for the survey of each hospital. We were fortunate enough finally to receive a reply from thirty-four of the thirty-five hospitals.

We have attempted in connection with slides to classify or demonstrate some of the returns which have been received. We have by no means been able to digest all of this and this is purely in the nature of a preliminary report.

Dr. Munns who has collected the data will illustrate with slides what we have put down. (An extensive report will be submitted later.)

President Hamill.—You have heard this very interesting report. Is there any discussion or does anyone care to ask any question regarding it? If not, we will continue with the report of the Committee on Relation to Section of the Diseases of Children of the American Medical Association. (No report.)

There was no report of the Committee on Relation to the White House Conference.

Report of the Committee on Relation of Academy to Philanthropic Agencies, Welfare Workers, Public Health Agencies, etc., by Dr. Edgar J. Huenekens, Chairman.

Dr. Huenekens.—This committee in filing its report last year, in which it outlined the general principles of the policy of the Academy to philanthropic agencies, welfare workers, public health agencies, etc., feels that it has fulfilled its function except to act as a committee of reference for individual problems as they arise.

This is our formal report. Among other things, your committee has considered the report of the Committee on the Cost of Medical Care and has noted that very little has been said about preventive pediatrics. The subject was briefly considered in the preliminary investigation but in the final summary of both majority and minority reports, preventive pediatrics was practically ignored. It was evidently considered not sufficiently important to merit mention.

Does this Society wish to inject itself into the highly controversial question of the cost of medical care? Your committee awaits instructions.

No report from the Committee on Nursing Education in Pediatrics.

No report from the Committee on School Health and School Health Education.

The Committee on Mental Hygiene

Dr. Bert I. Beverly.—Dr. Crothers was unable to be here so the report is in two parts; the first is presented by Dr. Crothers and the second part I will present.

Part I. The importance of getting some reasonable working knowledge of mental hygiene becomes more obvious as hard times continue. One thing sure is that "security" is almost nonexistent. Any one who has considered mental hygiene has learned that lack of a sense of stability and security is one of the major complications in rearing children.

With the evident increase in complications of living conditions, there is a decrease in the organized facilities for the care and study of maladjusted children by formal clinics. On the whole it seems perfectly clear that pediatricians are faced by an extraordinary situation which may easily be converted into a great opportunity.

A very large number of parents, psychologists and teachers have become convinced that extraordinary progress in child guidance has been made under psychiatric leadership. As a result of present conditions the need for guidance is increasing while the power of the organized clinics to maintain and increase service is diminishing. If we pediatricians can reach a clear understanding of our function in this whole field we may find that some effective basis of cooperation will help to tide over the rather critical period.

Certain suggestions are in order.

1. We should interview those responsible for units already in the field in our own communities. Many clinics depend upon local support and if, on examination, we approve, we can obviously help by discussing the whole situation with people who are interested. At present it is clear that pediatricians in general have not kept themselves informed and have no valid basis for judgment about child guidance clinics.

2. For the present, it is impossible to be satisfied that child guidance can be carried on by psychiatric clinics alone. Under these circumstances the pediatrician should not allow himself to be jockeyed into a position of cheerful skepticism. Too many entirely valid contributions have been made to allow disintegration of the movement in any community without a struggle.

3. Those opposed to the elaboration of certain clinics, to the overoptimism of certain psychiatrists and in general to the propaganda element can be assured that the times are fighting for simplification of the machinery.

The only suggestion the committee has to make is that the need is great to cooperate in every way with every reputable child guidance clinic in order to be sure that intelligent understanding on all sides is obtained. Out of it all, are great chances for improvement of pediatric practice.

Part II. The attitude assumed by the Society toward mental hygiene may have many far-reaching effects. Not only has extraordinary progress in child guidance been made under psychiatric leadership, as pointed out by Dr. Crothers, but child study has made important contributions to the whole field of psychiatry and greatly influenced pediatrics. The latter idea was recently emphasized by Cooley when he said, "Pediatrics has broadened its scope greatly since the time not many years ago when it was quite adequately defined as comprising infant feeding and the diseases of infancy and childhood. From that point it has grown rather rapidly but logically to arrogate to itself the supervision of all that pertains to physical and mental health and growth during the age period between birth and the end of adolescence." If this attitude is to be carried out in practice, mental hygiene must

be made a more important part of pediatrics. Such a possibility makes necessary a greater knowledge of psychiatry and mental hygiene by pediatricians. The education of doctors is, I believe, one of the accepted functions of the Society. In the case of mental hygiene it means the education of ourselves. To this end I would make the following suggestions:

1. The development of mental hygiene clinics as an integral part of children's hospitals and children's clinics.

2. Include mental hygiene courses and clinics in the pediatric department of medical schools.

3. Foster cooperation between the psychiatric and pediatric department such as already exist in urology, for instance.

A program of this kind would develop child guidance within the field of pediatrics. It would eliminate the big gap which often exists between agencies having widely different viewpoints toward children, which we recognize as not best for children.

President Hamill.—You have heard the report presented by Dr. Beverly. What is your wish in respect to it?

Dr. Cooley.—I move it be accepted. The motion was seconded and carried.

No report from the Committee on Clinical Investigation and Scientific Research.

President Hamill.—The final report is that of the Nominating Committee, to be presented by Dr. Veeder.

Dr. Veeder.—The Nominating Committee wishes to make the following report:

President—John Ruhräh, Baltimore, Maryland

President-Elect—Thomas B. Cooley, Detroit, Michigan

Secretary-Treasurer—Clifford G. Grulee, Evanston, Illinois

Member of Regional Committee for Region III to succeed Dr. Aldrich, whose term automatically expires in 1933, Dr. Henry F. Helmholz, Rochester, Minnesota.

President Hamill.—You have heard the nominations as presented by the Nominating Committee. Are there any further nominations?

Dr. Luecke.—I move the report of the Nominating Committee be approved and that the nominees as presented be elected.

The motion was seconded and carried.

President Hamill.—This completes the program of the business session, except that your outgoing President has the pleasure of presenting to you his successor, Dr. John Ruhräh of Baltimore, Maryland.

Dr. Ruhräh.—Fellow Members of the Academy, I am not going to make a speech to you today because I hope to do that next year at the annual meeting, but I do want to express my very deep sense of appreciation and gratitude for this honor and I do consider it a great honor to follow such men as Doctors Abt, Morse and Hamill and to be followed by such a man as Dr. Cooley. In thinking over why these men were chosen as Presidents, it is reasonably clear in most of the cases. Dr. Abt, and I think Dr. Morse, represent practitioners, consultants, authors and teachers with great distinction. Dr. Hamill has added to those qualifications his great work in sociologic medicine and infant welfare. My successor, while not a teacher, has been a consultant, practitioner and contributor, particularly in the line of blood diseases. I was wondering why I was chosen and I think the reason is that I have some very good friends on the Nominating Committee. I think perhaps it may also be partly due to the fact that I have tried to emphasize the cultural side of pediatrics as being more than a mere science. I want to thank all of you for my nomination.

President Hamill.—If there is no further business to come before the meeting, it will stand adjourned.

The meeting adjourned at 5 P.M.

News and Notes

The Georgia Pediatric Society held its annual meeting in Macon, May 10, 1933. Resolutions were adopted approving the activities of the American Academy of Pediatrics and pledging this organization's support in its work.

A motion providing for an annual scientific meeting of the **Georgia Pediatric Society** in addition to its business meeting was adopted. The first scientific meeting is to be held in Atlanta in the fall.

The following officers were elected for the coming year:

President: Dr. Joseph Yampolsky, Atlanta
Vice-President: Dr. W. W. Anderson, Atlanta
Secretary-Treasurer: Dr. Roger W. Dickson, Atlanta
President-Elect: Dr. Benjamin Bashinski of Macon

Book Reviews

Growth and Development of the Child. Part I: General Considerations. A publication of the White House Conference. The Century Company, 1932. Pp. 380.

This volume, the outcome of more than two years' work of the Committee on Growth and Development of the White House Conference, is a significant contribution of pediatrics, biology and sociology. Thirty-two authors contributed individually and collectively to the following general topics and their bearing on the growth and development of the child: Heredity, Prematurity, Human Types, Development of Physiological Stability, Temperature Regulation, Fatigue, Organized Physical Exercise for the Child (including the problem of Body Mechanics), the Biological Action of Light, Climate as It Affects Growth and Development, Seasonal Variations in Growth, Child Behavior, Socio-Economic Factors Influencing Growth and Development, Immunity and Age, and lastly, Some Important Diseases Affecting Growth and Development (tuberculosis, congenital syphilis, rickets, scurvy, hookworm and diabetes).

Among the authors are such well-known authorities in fundamental biology as Bardeen, Cannon, Davenport, Opie, Stenstrom and Todd and among pediatricians as Blackfan, Schlutz, Helmholz, Hess and Talbot. Each section or chapter, after being written by specialists, was subjected to review and criticism by the entire group. Hence, we have in this volume unusually clear and authoritative presentations of all the known factors involved in the growth and development of children. Even body mechanics, posture and physical training in relation to health and growth (where temptations to soar appear great) are appraised with proper perspective and regard to proved facts. Each chapter is well documented with literature references. Dr. Blackfan, the chairman of the committee producing this and its companion volumes, tells us in the introduction what the committee aimed to achieve; namely, the appraisal of existing knowledge concerning the growth and development of children from conception to maturity, the obstacles to growth that may be imposed by disease and economic circumstances, and indicating the places where data are lacking or inadequate, thus suggesting fruitful pathways to research. This broad aim appears to the reviewer to have been achieved to an unusual degree. The following quotation serves as an example of the broad scientific outlook, the common sense and courage in presenting generalizations and conclusions.

"Almost nothing has been done to prevent future generations arising from parents whose children must in all probability be doomed to misfortune and misery, a liability to society as well as to themselves. This is not a matter of class prejudice, for men know well that parenthood is beautiful only under conditions which make possible a heritage of physical and mental health and a favorable environment. Has the child a right to be well born? Has society any need that the child should have that right? Has the physician, when he undertakes to promote the health of the rising generation, the right to have under his care only children for whom healthy growth and satisfactory development is possible? Is the time coming when society must answer 'yes'? We believe so."

The volume should be on the shelf of every pediatrician and general practitioner who deals with children. More than this, it should be studied by every parent and teacher who has sufficient biological information to appreciate the facts and conclusions presented. Only in this way can the authors of this volume be adequately compensated for their exemplary labor of love in preparing this book, a labor of love to medicine and to society.

A. J. Carlson.

Comments

THE Third Annual Meeting of the Academy of Pediatrics in Chicago was attended by more than 150 members. The change to the first part of the week preceding rather than following the section meetings of the American Medical Association was an improvement. Considerable open time was allowed in this year's program so that members might take advantage of the Fair at Chicago. We suggest that the scientific program be increased next year to include two half-day sessions—even two round table conferences. The reports from the regional committees show tremendous activity on the part of the state units. It is becoming quite clear that the national organization can lay down only general policies. Each state has local problems and conditions in child health and hygiene, and the efforts by the state units must be directed according to local conditions and needs.

BOTH the Academy and the Section on Pediatrics of the American Medical Association approved the formation of an "American Board of Pediatrics" as outlined in the report of the Committee on Medical Education published in the April, 1933, issue. Representatives of these two groups and the American Pediatric Society which approved the report in May have been appointed and will select the personnel of the board.

ON JUNE 11th, more than a hundred and fifty representatives of the various specialties, specialty boards, National Board of Examiners, the Council of Medical Education of the American Medical Association and the Federation of State Board Examiners met in Milwaukee to discuss the question of the specialist. Drs. Cooley, Grulee, and Veeder represented the pediatric group. It was agreed upon to form a National Council of Specialty Qualifying Boards composed of two members from each specialty board and two representatives from each of the organizations mentioned above. A resolution was introduced into the House of Delegates of the American Medical Association on June 12 and favorably acted upon endorsing the "Specialty Board" as the best means of certifying to the competency of specialists and directing the Council of the American Medical Association to act with and further the work of these boards through the National Council. Committees on organization, standards for boards, and a Directory of Specialties were appointed. The general plan, as recommended for Pediatrics, has thus been decided upon and the various boards united for basic purposes while leaving to each group autonomy in its own field.

This development is of far-reaching importance in medicine. It means the elimination of the unqualified specialist and the gradual development on a nation-wide scale of regulations for the physician who restricts his field. Fundamentally it is a step forward in medical education such as was started in undergraduate education twenty years ago. A great many have expressed themselves of the view that ten years hence, or even less, it will be impossible to practice a specialty without a "certificate" which is based on educational standards.

THE Editorial Board of the Journal and the publishers wish to express their thanks and appreciation to the various individuals and organizations which made the Czerny Festschrift available. It is regretted that publication of two of the papers had to be postponed until this issue. They have been placed first so that the Festschrift papers appear in an uninterrupted group of 320 pages.

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